THE CLINICALLY NEGATIVE NECK IN ORAL SQUAMOUS CELL CARCINOMA

AN UPDATE ON PREOPERATIVE IMAGING AND FOLLOW-UP

Bart Matthijs Wensing

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PROEFSCHRIFT

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CHAPTER 1.0

General Introduction and Outline of this Thesis

Epidemiology

Squamous cell carcinoma of the oral cavity (SCCOC) accounts for about 500 newly diagnosed patients in the Netherlands each year; it represents 0,9% of all yearly newly diagnosed cancers and is the most common head and neck tumor in the Netherlands[1]. The number of patients diagnosed with this type of cancer has increased with an average of about 3.5% every year from 1989-1998[1]; this is mainly due to changes in populational build-up.

Etiology

The vast majority (about 90%) of OC cancers is of the squamous cell-type. Other types are malignant melanoma, mucoepidermoid carcinoma and adenoid cystic carcinoma. Use of alcohol, tobacco and chewing of betel nut, indisputedly are predisponding factors in case of squamous cell carcinoma[2-5]; other influencing factors might be the consumption of high amounts of salted meat and a high amount of fruit with a negative and a positive influence respectively[6, 7].

Anatomy

The oral cavity contains 7 anatomic subsites: lips (mucosal part), buccal mucosa, alveolar processes, floor of the mouth, anterior two thirds of the tongue ('oral tongue'), retromolar trigone and hard palate. The posterior boundary is an imaginary line drawn from the border between the hard and the soft palate towards the circumvillate papillae; the anterior boundary is formed by the vermilion border of the lips (***see figures 1 and 2***).

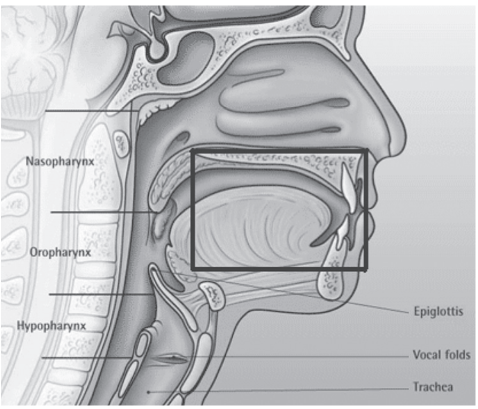

Figure 1: Oral cavity (box)

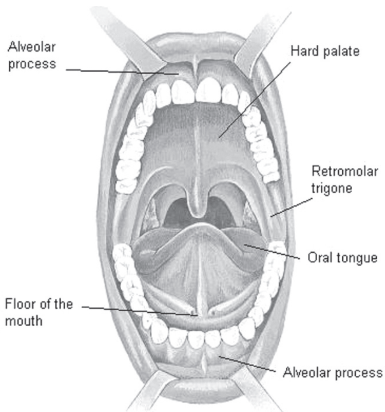

Figure 2: Oral cavity

One third of all lymphatic nodes a human possesses is situated in the head and neck region; dissemination of metastatic cells in cancer of the head and neck occurs mainly through lymphogenic spread and so these nodes play a crucial role: knowlegde of lymphatic drainage is eminent. When metastatic lymph nodes are present in the neck in SCCOC, overall survival decreases by 50%[8,9], so the need to diagnose (and treat) these nodes seems obvious.
Each patient suffering from head and neck squamous cell carcinoma (HNSCC) in the Netherlands is staged according to the international Tumor Node Metastasis (TNM) classification of the Union for International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC)[10]: both the primary tumor and the regional involvement of lymph nodes (in the neck) play an important role, as does the presence of distant metastatic spread. Neck staging is based on the size, side of the neck and number of affected nodes: the location of metastatic spread within the neck is not taken into account, although this might have a substantial influence on treatment and outcome. Neck levels are usually categorized according to a classification system developed by the American Academy of Otolaryngology & Head and Neck Surgery (***table 1*** and ***figure 3***[11]).

Level	Containing
Ia **Ib**	Submental nodes Submandibular nodes, containing submandibular gland
IIa **IIb**	Upper jugular nodes anterior to accessory nerve Upper jugular nodes posterior to accessory nerve
III	Mid-jugular nodes
IV	Lower jugular or supraclavicular nodes
V	Posterior triangle nodes
VI	Prelaryngeal nodes Pre-/paratracheal nodes

Table 1: Different neck levels and their nodes

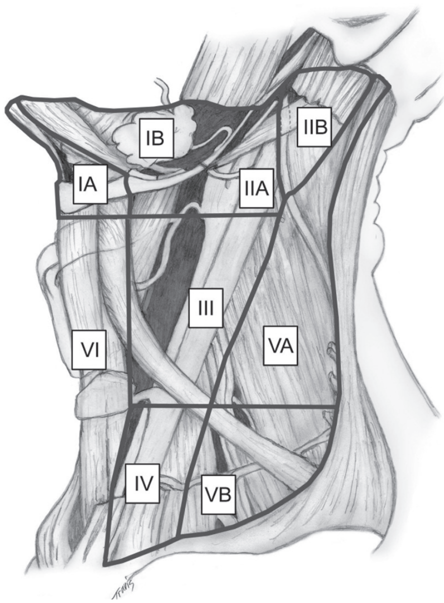

Figure 3: Anatomic location of neck levels

Lymphatic drainage

Basic studies by Lindberg[12] and Shah[13] demonstrated that SCCOC lymphatically tends to spread in a predictable way. According to Shah, who performed 192 radical neck dissections (RND) in patients suffering from SCCOC having a cN0 neck (with no clinically palpable metastases), these tumors mainly spread to level I-III[13]. These findings indicate that selective removal of the nodes in these specific levels should remove the vast majority of possibly tumor-positive nodes. However, a number of authors[14-16] emphasize that 'skip metastases' occur in a considerable amount of treated cN0 SCCOC patients: in these patients level I and II were not affected, while III and/or IV were. No consensus has been reached yet and the extent of neck dissection varies per medical center.

History of Neck Dissection

A century ago, in 1906, George Crile[17] was the first to introduce the RND, a surgical technique still used nowadays. This technique has been used for some 60 years to treat any neck of patients with any form of known HNSCC. In the early 60's, according to Ferlito[18], Suarez from Argentina started treating certain patients by the so-called 'functional neck dissection' (FND), as did Jesse and Ballantyne[19] in the United States of America. This approach was further popularized and introduced to Europe by Bocca[20].

Since then many forms of neck dissection have been described and advocated by various authors: certain kinds of neck pathology ask for certain kinds of neck dissection. In a widely accepted proposition by Weiss et al.[21] it is estimated, by decision analysis, that as long as rates above 20% of occult metastatic spread still are found during histopathologic examination of a cN0-neck in SCCOC, a prophylactic selective neck dissection (SND) should be performed. Since no preoperative staging technique repeatedly and by different authors was found to reach below this 20%-level, the search for a preoperative staging technique able to identify these clinically occult metastases goes on.

Nomenclature of different operating techniques

The RND, as described by Crile[17], encorporates the removal of all lymph nodes in neck levels I-V, applicable in all kinds of HNSCC. In RND the sternocleidomastoid muscle (SCM), internal jugular vein (IJV) and accessory nerve (AN) are removed. Removing these structures usually results in a high morbidity, covering diminished shoulder and neck movement and a decreased venous flow from the head[22, 23]. By preserving one, two or all of these structures in patients having cN0 necks, morbidity can be lowered; reason for this change were some detailed anatomical studies showing that neck structures like the SCM and the IJV were surrounded by fascia[24]. When this fascia and all overlying tissues are removed, the remaining structures probably will not harbour any metastases. A more reserved technique has shown to be accompanied by a lower morbidity and a higher quality of life[25]. After the introduction of SND, subclasses concerning both SND and RND rapidly were introduced, amongst which the 'modified radical neck dissection' (MRND). Generally nowadays a MRND comprises the removal of lymph nodes in region I-V; furthermore either the AN and/or the IJV and/or the SCM are being preserved. The type of neck dissection used depends on the location of the primary tumor plus its lymphatic drainage and the extent of neck disease. For a summary of the nomenclature see ***table 2.*** In 2002 Robbins et al.[11] updated their formerly introduced classification and proposed that all types of SND should for instance be called 'selective neck dissection comprising level I-III' instead of the formerly used term 'supraomohyoid neck dissection (SOHND)'.

Type of neck dissection	Levels cleared out	Structures sacrificed
Radical	I-V	AN, IJV and SCM
Modified Radical Type I	I-V	IJV and SCM
Modified Radical Type II	I-V	SCM
Modified Radical Type III (Conservative neck dissection)	I-V	None
Extended neck dissection	I-V + additional groups[1]	AN, IJV and SCM + extra[2]
Selective (supraomohyoid) neck dissection	I-III	None
Selective (extended supraomohyoid) neck dissection	I-IV	None
Selective (postero-lateral) neck dissection	II-V	None
Selective (lateral jugular) neck dissection	II-IV	None
Selective anterior (central) neck dissection	VI	None

Table 2: Types of neck dissection (modified from Robbins et al.[11])
1: groups like paratracheal nodes or anterior compartment nodes
2: structures not usually removed like carotid artery, hypoglossal nerve and/or vagus nerve

Staging-techniques

To treat a patient with SCCOC, one would like to know the extension of the disease, both local and regional, in order to adjust individualized therapy. Widely used preoperative neck staging techniques include palpation, ultrasound (US) with or without fine needle aspiration cytology (+/- FNAC), computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) scanning. Recently sentinel lymph node biopsy (SLNB) has been added as a diagnostic tool. For these preoperative techniques a wide range of sensitivities and specificities have been found; unfortunately no matter what test is being used, false-negative rates are still high. Roughly 20 to 30 percent of the cN0-necks (meaning that preoperatively no proof of metastatic spread was present during palpation and any kind of imaging) contain histopathologically proven, metastatic lymph nodes in surgical resection specimens[26-28]. By preoperative investigation both high sensitivities and specificities are reached, but never combined in one technique. When more strict criteria for defining metastases are applied (raising specificity), this inevitably leads to a drop in sensitivity (and the other way around as well). Postoperative staging by means of histopathological examination still counts as the 'golden standard'.

Histopathologic examination

Histopathologic examination in most cases consists of routine hemotoxylin- and eosin staining (H&E; mostly performed on slices of 2 to 3 mm with a thickness of 4μ). This technique renders less detailed and so probably less reliable information than for instance the examination of more slices per lymphnode (up to 0,5 mm per coupe) and/or the addition of immunohistochemistry[29]. Some authors even state that if these latter techniques would be standardized, the sensitivity of a lot of preoperative staging techniques would probably be lowered further[30].

US +/-FNAC

Ultrasound can easily be combined with FNAC resulting in a high specificity being reached. Some authors, such as van den Brekel et al.[31, 32], have reached good results with US +/-FNAC in the cN0-neck. This technique is based on tracking the largest nodes (which don't have to be suspicious) or suspicious nodes on both sides of the neck by US and punctuate them for cytologic examination: minimal diameter of nodes to be punctured is 3-4 mm. Sensitivity for this staging technique in cN0 SCCOC, still only reaches 76%[32] and not all authors reach these high percentages[33, 34].

CT and MRI

Along with US, CT and MRI are long-known staging techniques; more thoroughly than by US, morphological characteristics of nodes can be depicted and interpreted. Also, CT and MRI images are more widely interpretable, not being dynamic imaging techniques. The presence or absence of extracapsular spread (ECS), a reknown bad prognosticator[35, 36], can be estimated by both CT and MRI. Factors that also might indicate metastatic involvement of nodes are size (>10 mm smallest diameter), shape of the node (metastatic nodes tend to have a more rounded shape) and presence of irregular contrast enhancement due to tumor necrosis[37]. The latter characteristic is usually not present in small metastatic nodes; this explains why, in cN0-necks, size- and shape-criteria are mainly used for assessing neck status. However, any chosen size criterium will be a compromise between sensitivity and specificity: which axis to measure and which cutoff-points to use have been subject to a number of studies[38-41]. When focusing on staging of the palpably N0-neck, regardless of the kind of primary head and neck tumor, sensitivities and specificities for CT range from 40-83% and 78-100% respectively[37]. These percentages range from 55-80 and 82-92 respectively for conventional MRI[37, 42].

FDG-PET

The latest non-invasive diagnostic tool introduced to identify occult metastases is the Fluoro Deoxy Glucose (FDG)-PET-scan: a radioactively labeled glucose-derivative is injected into the bloodstream and accumulates in locations with a high glucose-usage. Tumorous cells are known to consume a higher amount of glucose than non-tumorous cells and so will be depicted by the gamma-camera. In imaging primary N+ HNSCC FDG-PET has shown to be an accurate staging tool[43-45].

Sentinel lymph node biopsy

A minimally invasive technique coming up is SLNB, as introduced by Morton et al.[46] in melanoma. This technique is based on imaging the route of lymphatic flow. When a radio-active contrasting fluid is injected near the primary tumor, it will be flushed out by the lymphatic system in the vicinity of the tumorsite; when images are being made with certain intervals, the flow and direction of the lymphe, comparable to possible metastatic flow from the tumor, can preoperatively be pictured by means of lymphoscintigraphy or (more recently adapted) single photon emission computed tomography (SPECT). In this way the first echelon is discovered, peroperatively confirmed by a hand-held gamma probe and subsequently excised. Histopathological examination consisting of multi-slice sectioning and immunohistochemistry is performed: when metastatic proof is found, the second echelon will be subsequently treated. With absent proof of metastatic disease, the procedure is terminated. Paleri et al.[47] performed a meta-analysis of studies regarding SLNB; their study ‘provided a firm evidence base for forthcoming trials on the role of SLNB in head and neck cancer’. Recently, different authors have advocated the use of SLNB in low stage SCCOC[48-50]. Future results will clarify the role of SLNB in SCCOC. For an overview of preoperative staging techniques, see ***table 3.***

Staging Technique	Sensitivity (%)	Specificity (%)	Accuracy (%)
Palpation	74	81	59 – 76
US	58 – 97	32 – 78	68 – 83
US +/-FNAC	48 – 98	95 – 100	79 – 89
CT	49 – 83	74 – 100	66 – 89
MRI	33 – 64	69 – 96	66 – 90
FDG- PET	0 – 100	50 – 100	63 – 100

Table 3*:* Different staging techniques and their respective sensibilities, specificities and accuracies[27-34]

Histopathological tumor characteristics

When looked at ways to predict whether a tumor will metastasize or not, whether there is a high or low chance at locoregional recurrence and how to estimate survival, much research has also been done in the field of primary tumor characteristics. If an excised cN0 primary SCCOC or a preoperative biopsy could be examined for several known prognostic characteristics, a neck dissection could for instance be performed only if tumorcharacteristics would indicate a high tendency to metastasize. Size (pT-stage), presence of perineural spread, angiolymphatic invasion, diffuse growing patterns, grade of differentiation and tumor depth have all been mentioned as possible prognosticators in predicting survival and/or locoregional recurrence[9, 51-58].

Biomarkers

Tumoral development is based on changes in normal cellular processes (like proliferation, differentiation, cell adhesion and apoptosis), leading to uncontrolled growth and/or invasion of surrounding structures and/or the ability to metastasize. The latter option represents a complex cascade of events, including proliferation, migration through interstitial cell matrices, invasion of lymph- and blood vessels, finally reaching a lymph node or distant organ and growing out at the new site. The assumption that characteristics of the primary tumor mainly determine its probability to spread metastatically, could be used as a predictive source of tumoral behaviour and so could possibly influence treatment of the neck in SCCOC. Nowadays simple light microscopy, immunohistochemistry, Southern blot techniques, polymerase chain reaction (PCR) and fluorescence in situ hybridization (FISH) are available to identify histological and genetic tumoral features.
A biopsy-sample of the primary tumor might give the information on which treatment

of the neck could be based. In SCCOC and oropharyngeal SCC Roepman et al.[59] presented an independently validated primary tumor expression signature set of 102 different predictor genes that could reliably detect the presence of metastases in regional lymph nodes. It performed better than current clinical staging techniques. A multicenter validation study is currently being performed.

Conclusions

Treatment of cancer of the head and neck has undergone quite some changes in the past century; from relative overtreatment to treatment that is more adjusted individually, leading to less morbidity and a higher quality of life with (slightly) improved survival. Probably a great deal of patients suffering from SCCOC with a cN0-neck will eventually not be treated by a neck dissection because the percentage of occult neck metastases will be below 20%. However, before this point is reached, a more accurate preoperative staging technique will have to be found, which can be easily applied in any center for head and neck surgery.

Goal and outline of this thesis

Goal of this thesis is to analyze the results of our current preoperative workup regarding the neck in cN0 SCCOC consisting of palpation and US (+/- FNAC) along with evaluation of postoperative results in terms of follow-up, survival and locoregional recurrence rates.
Another goal is to investigate whether the percentage of occult metastatic spread found by postoperative histopathological examination can be lowered to less than the proposed 20%[21] by means of new preoperative imaging techniques.
In **Chapter 2** we retrospectively review the treatment regime described above in 224 patients with cN0 SCCOC, with special emphasis on the results of US (+/- FNAC) related to postoperative histopathological findings.
In **Chapter 3 part I** we prospectively analyze a group of 30 SCCOC patients with focus on the preoperative assessment of the cN0 neck by FDG-PET. Refinement of the used FDG-PET scanning technique is described in **part II**.
Chapter 4 describes a pilot study regarding the use of a new MRI contrast agent (USPIO) in 11 patients suffering from cN0 SCCOC.
Chapter 5 describes overall and disease-specific survival in 197 treated patients with cN0 SCCOC, after 5 years of follow-up and mainly focuses on the necessity of a strict follow-up regime.

Chapter 6 identifies histopathological tumor and neck characteristics which could have a prognostic value regarding recurrent disease and disease-free survival in a group of 197 cN0 SCCOC patients.

Reference List

1. Knegt PP, Keus RB, Roodenburg JL. [The practice guideline 'Carcinoma of the oral cavity and oropharynx']. Ned Tijdschr Geneeskd 2006 Jan 14;150(2):83-8.
2. Schildt EB, Eriksson M, Hardell L, et al. Oral snuff, smoking habits and alcohol consumption in relation to oral cancer in a Swedish case-control study. Int J Cancer 1998 Jul 29;77(3):341-6.
3. Blot WJ, McLaughlin JK, Winn DM, et al. Smoking and drinking in relation to oral and pharyngeal cancer. Cancer Res 1988 Jun 1;48(11):3282-7.
4. de Stefani E, Boffetta P, Oreggia F, et al. Smoking patterns and cancer of the oral cavity and pharynx: a case-control study in Uruguay. Oral Oncol 1998 Sep;34(5):340-6.
5. Lin WJ, Jiang RS, Wu SH, et al. Smoking, alcohol, and betel quid and oral cancer: a prospective cohort study. J Oncol 2011;2011:525976.
6. de Stefani E, Oreggia F, Ronco A, et al. Salted meat consumption as a risk factor for cancer of the oral cavity and pharynx: a case-control study from Uruguay. Cancer Epidemiol Biomarkers Prev 1994 Jul;3(5):381-5.
7. de Stefani E, Deneo-Pellegrini H, Mendilaharsu M, et al. Diet and risk of cancer of the upper aerodigestive tract--I. Foods. Oral Oncol 1999 Jan;35(1):17-21.
8. Snow GB, Annyas AA, van Slooten EA, et al. Prognostic factors of neck node metastasis. Clin Otolaryngol 1982 Jun;7(3):185-92.
9. Leemans CR, Tiwari R, Nauta JJ, et al. Recurrence at the primary site in head and neck cancer and the significance of neck lymph node metastases as a prognostic factor. Cancer 1994 Jan 1;73(1):187-90.
10. Sobin LH, Fleming ID. TNM Classification of Malignant Tumors, fifth edition (1997). Union Internationale Contre le Cancer and the American Joint Committee on Cancer. Cancer 1997 Nov 1;80(9):1803-4.
11. Robbins KT, Clayman G, Levine PA, et al. Neck dissection classification update: revisions proposed by the American Head and Neck Society and the American Academy of Otolaryngology-Head and Neck Surgery. Arch Otolaryngol Head Neck Surg 2002 Jul;128(7):751-8.
12. Lindberg R. Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. Cancer 1972 Jun;29(6):1446-9.
13. Shah JP, Candela FC, Poddar AK. The patterns of cervical lymph node metastases from squamous carcinoma of the oral cavity. Cancer 1990 Jul 1;66(1):109-13.
14. Byers RM, Weber RS, Andrews T, et al. Frequency and therapeutic implications of "skip metastases" in the neck from squamous carcinoma of the oral tongue. Head Neck 1997 Jan;19(1):14-9.
15. Crean SJ, Hoffman A, Potts J, et al. Reduction of occult metastatic disease by extension of the supraomohyoid neck dissection to include level IV. Head Neck 2003 Sep;25(9):758-62.
16. Medina JE, Byers RM. Supraomohyoid neck dissection: rationale, indications, and surgical technique. Head Neck 1989 Mar;11(2):111-22.
17. Crile G. Landmark article Dec 1, 1906: Excision of cancer of the head and neck. With special reference to the plan of dissection based on one hundred and thirty-two operations. By George Crile. JAMA 1987 Dec 11;258(22):3286-93.
18. Ferlito A, Robbins KT, Shaha AR, et al. Current considerations in neck dissection. Acta Otolaryngol 2002 Apr;122(3):323-9.

19. Jesse RH, Ballantyne AJ, Larson D. Radical or modified neck dissection: a therapeutic dilemma. Am J Surg 1978 Oct;136(4):516-9.
20. Bocca E, Pignataro O, Sasaki CT. Functional neck dissection. A description of operative technique. Arch Otolaryngol 1980 Sep;106(9):524-7.
21. Weiss MH, Harrison LB, Isaacs RS. Use of decision analysis in planning a management strategy for the stage N0 neck. Arch Otolaryngol Head Neck Surg 1994 Jul;120(7):699-702.
22. Ewing MR, Martin H. Disability following radical neck dissection; an assessment based on the postoperative evaluation of 100 patients. Cancer 1952 Sep;5(5):873-83.
23. Shone GR, Yardley MP. An audit into the incidence of handicap after unilateral radical neck dissection. J Laryngol Otol 1991 Sep;105(9):760-2.
24. Ferlito A, Buckley JG, Shaha AR, et al. Rationale for selective neck dissection in tumors of the upper aerodigestive tract. Acta Otolaryngol 2001 Jul;121(5):548-55.
25. Kuntz AL, Weymuller EA, Jr. Impact of neck dissection on quality of life. Laryngoscope 1999 Aug;109(8):1334-8.
26. Pitman KT, Johnson JT, Myers EN. Effectiveness of selective neck dissection for management of the clinically negative neck. Arch Otolaryngol Head Neck Surg 1997 Sep;123(9):917-22.
27. Myers LL, Wax MK, Nabi H, et al. Positron emission tomography in the evaluation of the N0 neck. Laryngoscope 1998 Feb;108(2):232-6.
28. van den Hoogen FJ, Manni JJ. Value of the supraomohyoid neck dissection with frozen section analysis as a staging procedure in the clinically negative neck in squamous cell carcinoma of the oral cavity. Eur Arch Otorhinolaryngol 1992;249(3):144-8.
29. Civantos FJ, Gomez C, Duque C, et al. Sentinel node biopsy in oral cavity cancer: correlation with PET scan and immunohistochemistry. Head Neck 2003 Jan;25(1):1-9.
30. Brouwer J, de Bree R, Comans EF, et al. Positron emission tomography using [18F]fluorodeoxyglucose (FDG-PET) in the clinically negative neck: is it likely to be superior? Eur Arch Otorhinolaryngol 2004 Oct;261(9):479-83.
31. van den Brekel MW, Castelijns JA, Stel HV, et al. Modern imaging techniques and ultrasound-guided aspiration cytology for the assessment of neck node metastases: a prospective comparative study. Eur Arch Otorhinolaryngol 1993;250(1):11-7.
32. van den Brekel MW, Castelijns JA, Stel HV, et al. Occult metastatic neck disease: detection with US and US-guided fine-needle aspiration cytology. Radiology 1991 Aug;180(2):457-61.
33. Takes RP, Righi P, Meeuwis CA, et al. The value of ultrasound with ultrasound-guided fine-needle aspiration biopsy compared to computed tomography in the detection of regional metastases in the clinically negative neck. Int J Radiat Oncol Biol Phys 1998 Mar 15;40(5):1027-32.
34. Righi PD, Kopecky KK, Caldemeyer KS, et al. Comparison of ultrasound-fine needle aspiration and computed tomography in patients undergoing elective neck dissection. Head Neck 1997 Oct;19(7):604-10.
35. Myers JN, Greenberg JS, Mo V, et al. Extracapsular spread. A significant predictor of treatment failure in patients with squamous cell carcinoma of the tongue. Cancer 2001 Dec 15;92(12):3030-6.
36. Greenberg JS, Fowler R, Gomez J, et al. Extent of extracapsular spread: a critical prognosticator in oral tongue cancer. Cancer 2003 Mar 15;97(6):1464-70.

37. van den Brekel MW. Lymph node metastases: CT and MRI. Eur J Radiol 2000 Mar;33(3):230-8.
38. Friedman M, Roberts N, Kirshenbaum GL, et al. Nodal size of metastatic squamous cell carcinoma of the neck. Laryngoscope 1993 Aug;103(8):854-6.
39. Don DM, Anzai Y, Lufkin RB, et al. Evaluation of cervical lymph node metastases in squamous cell carcinoma of the head and neck. Laryngoscope 1995 Jul;105(7 Pt 1):669-74.
40. van den Brekel MW, Stel HV, Castelijns JA, et al. Cervical lymph node metastasis: assessment of radiologic criteria. Radiology 1990 Nov;177(2):379-84.
41. van den Brekel MW, Castelijns JA, Snow GB. The size of lymph nodes in the neck on sonograms as a radiologic criterion for metastasis: how reliable is it? AJNR Am J Neuroradiol 1998 Apr;19(4):695-700.
42. Wide JM, White DW, Woolgar JA, et al. Magnetic resonance imaging in the assessment of cervical nodal metastasis in oral squamous cell carcinoma. Clin Radiol 1999 Feb;54(2):90-4.
43. Stokkel MP, ten Broek FW, van Rijk PP. Preoperative assessment of cervical lymph nodes in head and neck cancer with fluorine-18 fluorodeoxyglucose using a dual-head coincidence camera: a pilot study. Eur J Nucl Med 1999 May;26(5):499-503.
44. Schmid DT, Stoeckli SJ, Bandhauer F, et al. Impact of positron emission tomography on the initial staging and therapy in locoregional advanced squamous cell carcinoma of the head and neck. Laryngoscope 2003 May;113(5):888-91.
45. Hannah A, Scott AM, Tochon-Danguy H, et al. Evaluation of 18 F-fluorodeoxyglucose positron emission tomography and computed tomography with histopathologic correlation in the initial staging of head and neck cancer. Ann Surg 2002 Aug;236(2):208-17.
46. Morton DL, Wen DR, Foshag LJ, et al. Intraoperative lymphatic mapping and selective cervical lymphadenectomy for early-stage melanomas of the head and neck. J Clin Oncol 1993 Sep;11(9):1751-6.
47. Paleri V, Rees G, Arullendran P, et al. Sentinel node biopsy in squamous cell cancer of the oral cavity and oral pharynx: a diagnostic meta-analysis. Head Neck 2005 Sep;27(9):739-47.
48. Civantos FJ, Zitsch RP, Schuller DE, et al. Sentinel lymph node biopsy accurately stages the regional lymph nodes for T1-T2 oral squamous cell carcinomas: results of a prospective multi-institutional trial. J Clin Oncol 2010 Mar 10;28(8):1395-400.
49. Murer K, Huber GF, Haile SR, et al. Comparison of morbidity between sentinel node biopsy and elective neck dissection for treatment of the n0 neck in patients with oral squamous cell carcinoma. Head Neck 2010 Nov 29.
50. Stoeckli SJ, Alkureishi LW, Ross GL. Sentinel node biopsy for early oral and oropharyngeal squamous cell carcinoma. Eur Arch Otorhinolaryngol 2009 Jun;266(6):787-93.
51. Pentenero M, Gandolfo S, Carrozzo M. Importance of tumor thickness and depth of invasion in nodal involvement and prognosis of oral squamous cell carcinoma: a review of the literature. Head Neck 2005 Dec;27(12):1080-91.
52. Chen TY, Emrich LJ, Driscoll DL. The clinical significance of pathological findings in surgically resected margins of the primary tumor in head and neck carcinoma. Int J Radiat Oncol Biol Phys 1987 Jun;13(6):833-7.
53. Parsons JT, Mendenhall WM, Stringer SP, et al. An analysis of factors influencing the outcome of postoperative irradiation for squamous cell carcinoma of the oral cavity. Int J Radiat Oncol Biol Phys 1997 Aug 1;39(1):137-48.

54. Patel RS, Clark JR, Dirven R, et al. Prognostic factors in the surgical treatment of patients with oral carcinoma. ANZ J Surg 2009 Jan;79(1-2):19-22.
55. Ravasz LA, Slootweg PJ, Hordijk GJ, et al. The status of the resection margin as a prognostic factor in the treatment of head and neck carcinoma. J Craniomaxillofac Surg 1991 Oct;19(7):314-8.
56. Fagan JJ, Collins B, Barnes L, et al. Perineural invasion in squamous cell carcinoma of the head and neck. Arch Otolaryngol Head Neck Surg 1998 Jun;124(6):637-40.
57. Rahima B, Shingaki S, Nagata M, et al. Prognostic significance of perineural invasion in oral and oropharyngeal carcinoma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2004 Apr;97(4):423-31.
58. Liao CT, Lin CY, Fan KH, et al. Identification of a High-Risk Group Among Patients With Oral Cavity Squamous Cell Carcinoma and pT1-2N0 Disease. Int J Radiat Oncol Biol Phys 2010 Nov 13.
59. Roepman P, Wessels LF, Kettelarij N, et al. An expression profile for diagnosis of lymph node metastases from primary head and neck squamous cell carcinomas. Nat Genet 2005 Feb;37(2):182-6.

CHAPTER 2.0

Assessment of preoperative ultrasonography of the neck and elective neck dissection in patients with oral squamous cell carcinoma

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Abstract

Objective

Estimating the value of our preoperative workup in the treatment of patients with clinically N0 (cN0) squamous cell carcinoma of the oral cavity (SCCOC).

Methods

Results of preoperative palpation, ultrasound (US) and ultrasound-guided fine needle aspiration cytology (FNAC) were compared to the histological findings after unilateral or bilateral elective selective neck dissection of level I-III (SND I-III) in patients with cN0 SCCOC.

Results

Occult metastases were detected in 50 (22%) out of the 224 cN0 patients. No metastases were found beyond level III in extended neck dissections. T1N0M0 tumors and T2N0M0 tumors metastasized in 8 out of 77 cases (10%) and 32 out of 112 (29%) cases, respectively.

Conclusions

Staging of the cN0 neck by palpation and US (+/- ultrasound-guided FNAC) missed occult lymph node metastases in 22% of the patients with SCCOC. The use of SND I-III therefore still is warranted. Frozen section sampling seemed to be redundant in this selected group of patients, because no additional metastases were found in extended neck dissection specimens. It might not be necessary to perform elective neck dissection in patients with T1 tumors.

Introduction

The most important prognostic factor in patients with oral cavity squamous cell carcinoma is the presence or absence of cervical metastases. When there was metastatic spread to the cervical lymphnodes, survival rates decreased by approximately 50%[1-3]. Until now, imaging techniques, such as ultrasound (US), computerized tomography (CT) and magnetic resonance imaging (MRI), have shown inadequate predictability of cervical metastases[4]. In contrast, minimally invasive techniques, e.g. ultrasound-guided fine needle aspiration cytology (ultrasound-guided FNAC), had higher sensitivity and specificity than the above-mentioned imaging techniques, although only in experienced hands[5]. Sentinel lymph node biopsy (SLNB) has not yet achieved the status of "standard of care"[6]; it is still considered as an experimental technique. Elective surgical procedures to detect potential occult metastases are currently preferable to a 'wait and see' policy (or primary radiotherapy). In the clinically node negative neck, elective surgical dissection forms part of the standard approach, because the risk of occult metastatic spread was found to exceed 20%[7]. The type of neck dissection used in elective surgery has changed over the years from radical neck dissection (as described by Crile[8]) to more selective types of neck dissection. Reasons behind these changes were greater understanding of regional lymph drainage patterns[9] and concerns about postoperative morbidity. In patients with oral cavity carcinoma, selective neck dissection of level I-III (SND I-III; former supraomohyoid neck dissection) is the preferred technique. Besides its staging ability, it might also form a therapeutic option to control minimal neck disease in a selected group of patients[10,11]. However, some authors advocated the use of an extended neck dissection that includes level IV, or even modified radical neck dissection (MRND) to increase the detection rate of 'skip metastases'[12,13]. In this study, we investigated the diagnostic and therapeutic value of the SND I-III after the patients had been staged node negative by palpation, US and on indication, ultrasound-guided FNAC of one or more nodes.

Materials and Methods

Data were available on a consecutive series of patients with histopathologically proven squamous cell carcinoma of the oral cavity who had been treated at the Head and Neck Centre of the University Hospital Nijmegen between 1 January 1992 and 1 December 2004. All the cN+ patients were excluded from the study because they had not undergone SND I-III. In addition, patients who had been diagnosed with any form of head and neck carcinoma in the previous 5 years were excluded. Patients were included if they had a clinically and radiologically node negative neck and had undergone SND I-III as part of their surgical treatment. Preoperative TNM staging had been performed according to the system of the International Union Against Cancer[14]. Some of the patients had an indication for ultrasound-guided FNAC, because US had found suspicious or enlarged lymph nodes (smallest axial diameter >5 mm). Unilateral SND I-III had been performed on the affected side, or bilateral when the tumor crossed the midline. All the operations had been carried out by surgeons at our Head and Neck Centre, according to the procedure described by Medina[15]. Suspicious nodes and/or the largest jugulodigastric and most distal jugulo-omohyoid node were sampled and sent for frozen sectioning together with the dissection specimen. If frozen sectioning showed metastatic disease, SND I-III was routinely extended to MRND. An exception to this rule was one single metastatic node without extracapsular spread in level I. The neck dissection specimen was marked so that levels could be identified by the pathologist. Standard pathological examination of the neck dissection specimen consisted of Haematoxylin and Eosin staining, node count with standard sectioning and measuring the size of the metastatic deposits in all the affected nodes. Two or more positive nodes in the neck dissection specimen and/or presence of extracapsular spread were indications for postoperative radiotherapeutic treatment of the neck.

Results

The study included 224 patients with 247 SND I-III specimens. There were 145 men and 79 women, with a mean age of 61 years at the time of surgery (range 27-90 years). The distributions of localisation and clinical T-staging of the tumors are shown in ***table 1***.

Primary tumor site (No. of patients)	T1	T2	T3	T4	Total
Floor of mouth	24	51	6	4	85
Lateral Tongue	41	44	13	0	98
Alveolar process	2	5	1	5	13
Retromolar trigone	9	8	0	6	23
Buccal mucosa	1	4	0	0	5
Total	**77**	**112**	**20**	**15**	**224**

Table 1: Primary tumor localisations and preoperative stages (No. of patients)

All the patients had undergone ultrasound examination; in 2 patients whose tumor crossed the midline, only one side of the neck had been examined. ***Figure 1*** shows an overview of the patients who had indications for ultrasound-guided FNAC. In the majority of these patients it was not possible to establish whether the cytology obtained during this procedure was from nodes in the same levels as those found to contain metastases during histopathological examination. There was only one positive histopathological result out of 7 inconclusive punctures. It revealed 2 metastases: one in level I (0.8 x 0.7 cm) and one in level II (1.0 x 0.8 cm). The tumor deposit in the first positive lymph node consisted of multiple micrometastases, whereas the deposit in the second (level II) positive lymph node had a diameter of 1.2 mm. Thus, initial ultrasound-guided FNAC was false-negative in 22%, while inconclusive node puncture was positive on histopathological examination in 14%.

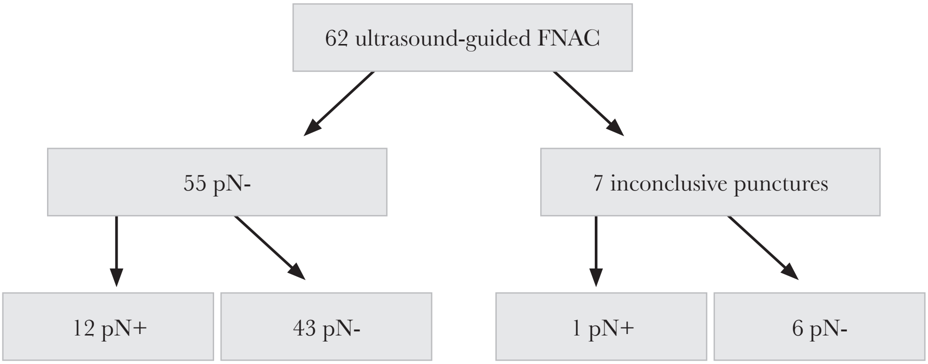

Figure 1: Results of ultrasound-guided FNAC

A total of 224 patients had undergone 247 SND I-IIIs: 96 on the right side, 105 on the left side and 23 bilateral. ***Figure 2*** shows an overview of the surgical procedures, including extensions to MRND and the histopathological findings.

In 6 out of the 24 frozen section-positive necks, not only the frozen section node was positive: 5 necks also contained 2 levels with one metastatic node, while 1 neck also contained 3 levels with single metastatic nodes. In six cases, the dissections had not been extended to MRND, because metastatic spread was only found in level I and frozen section in lower level nodes was negative. Three dissections (frozen section-negative) had also been extended to MRND owing to strong perioperative suspicion of metastatic spread. Also, two bilateral SND I-IIIs had been modified to unilateral MRND and contralateral SND I-III due to strong perioperative suspicion of metastases. Histopathological examination revealed metastases on the MRND side in these latter patients, although frozen section had been negative. A total of 23 SND I-IIIs had thus been extended (9% of necks) to MRND. Metastases were not found outside levels I-III in any of these extended neck dissections.

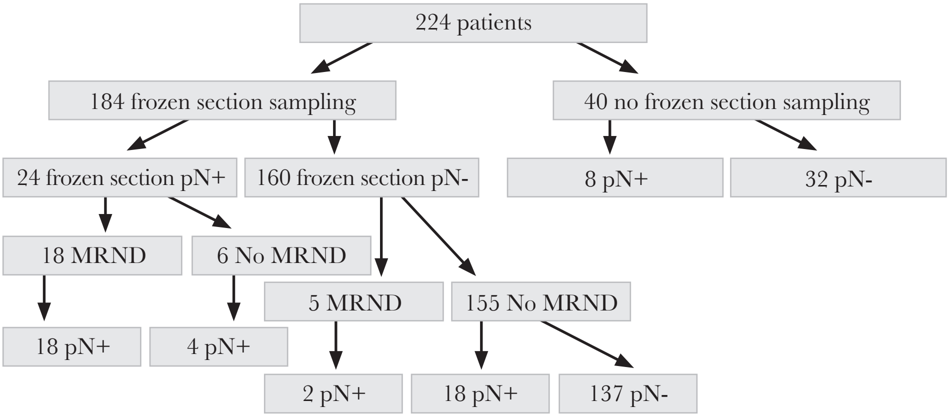

Figure 2: Neck dissections (N = 224) and the pN-status

Histopathological proof of metastatic squamous cell carcinoma in one or more lymph nodes was found in 50 of the specimens (22%); thus, 24 out of 50 (48%) positive specimens had been identified correctly by frozen section sampling. MRND had been performed on 20 of the 50 pN+ necks and 14 of them had also received postoperative radiotherapy. Based on the histopathological findings, 25 of the remaining 30 pN+ patients had received postoperative radiotherapy.
In the 50 positive specimens levels I, II and III had been affected in 23 (46%), 31 (62%) and 11 (22%) necks, respectively. When level III had been the only pN+ level, postoperative radiotherapy was administered. Positive specimens had been revealed in 8 out of the 21 bilateral SND I-IIIs. All but one had comprised a single node in a single level on one side (5 in level I, 2 in II, 1 in III). The remaining specimen had been positive bilaterally, with 2 positive nodes on the left side of the MRND specimen (levels I and II) and 1 positive node on the right side (SND I-III). Primary tumor localisations and T-stages in relation with the affected neck levels are shown in ***tables 2 and 3***, respectively.

Primary tumor site (No. of positive neck specimens)	**Level(s) affected**							
	I	II	III	I + II	I + III	II + III	I-III	**% occult metastases**
Floor of mouth	10	5	3	2*	1	0	0	25
Lateral tongue	1	11	2	3	0	2	1	20
Alveolar process	1	1	0	2	1	0	0	38
Retromolar trigone	0	2	0	1	0	1	0	17
Buccal mucosa	0	0	0	0	0	0	0	0

Table 2: Tumor localisations and the affected lymph node levels in 50 positive neck specimens (* = positive bilateral neck dissection)

TN-classification (No. of patients)	Level(s) affected							
	I	II	III	I + II	I + III	II + III	I-III	% occult metastases
T1	1	6	0	1	0	0	0	10
T2	8	11	5	3	1	3	1	29
T3	2	1	0	2	0	0	0	25
T4	1	1	0	2*	1	0	0	33
Total	12	19	5	8	2	3	1	22

Table 3: Tumor stages and the affected lymph node levels in 224 patients (* = positive bilateral neck dissection)

Tables 4 and 5 show the numbers of occult metastases in the patients with T1 and T2 tumors, respectively. In T1 oral cavity tumors the risk of occult metastases was about 10% (8 out of 77 T1 tumors). In T2 tumors the risk increased to about 30% (32 out of 112 T2 tumors). Tumor-positive nodes were subdivided into three groups according to the smallest diameter of the metastatic deposit inside the lymph node: 0-5 mm, 6-10 mm and >10 mm. These dimensions had been recorded in only 44 pN+ necks.

Tumor localisation (No. of patients)	Neck status		
	pN0	pN+	% pN+
Floor of mouth	22	2	8%
Lateral tongue	36	5	12%
Retromolar trigone	8	1	11%
Alveolar process	2	0	0%
Buccal mucosa	1	0	0%

Table 4: T1N0M0 tumors and the histopathological neck status

Tumor localisation (No. of patients)	Neck status		
	pN0	pN+	% pN+
Floor of mouth	35	16	31%
Lateral tongue	32	12	27%
Retromolar trigone	5	3	38%
Alveolar process	3	2	40%
Buccal mucosa	4	0	0%

Table 5: T2N0M0 tumors and the histopathological neck status

Tables 6 and 7 show these subgroups in relation with the clinical T-stage and the localisation of the primary tumor, respectively.

TN classification tumor (No. of specimens)	Smallest diameter of metastatic deposit		
	0-5 mm	6-10 mm	>10 mm
T1	5 (63%)	2 (25%)	1 (12%)
T2	22 (81%)	5 (19%)	0
T3	3 (60%)	2 (40%)	0
T4	4 (100%)	0	0
Total	34 (77%)	9 (20%)	1 (23%)

Table 6: Tumor stages and size of the metastatic part in the lymph nodes

Tumor localisation (No. of specimens)	Smallest diameter of metastatic deposit		
	0-5 mm	6-10 mm	>10 mm
Floor of the mouth	18 (86%)	3 (14%)	0
Lateral side of oral tongue	12 (71%)	5 (29%)	0
Retromolar trigone	2 (67%)	0	1 (33%)
Alveolar process	2 (67%)	1 (33%)	0
Total	34 (77%)	9 (20%)	1 (2%)

Table 7: Tumor localisation and size of the metastatic part in the lymph nodes

Discussion

An earlier study at our centre[16] showed that SND I-III with frozen section sampling was a useful tool to manage the cN0 neck in patients with primary squamous cell carcinoma of the oral cavity. In the present study, US of the neck (+/- ultrasound-guided FNAC) had been added to the standard preoperative evaluation protocol. Our group of 224 patients with cN0 oral cavity squamous cell carcinoma had all undergone SND I-III. The addition of ultrasonographic evaluation of the neck led to reductions in the percentage of missed occult metastatic lymph nodes from 31% in our initial study to 22%, or even to 20% when the focus was on individual necks.

There was a significant difference (p=0.016) in the risk of developing occult metastases between T1 (10%) and the other T-stages (T2 = 29% T3 = 25% and T4 = 33%). Tumor localisation seemed to have less influence.

After ultrasonographic evaluation of the neck, SND I-III found occult metastatic lymph nodes in 22% of the patients (50 out of the 224). This rate was more favourable than that reported in a number of studies[9,17] that evaluated the neck with palpation or CT/MRI, but without US. US (+/- FNAC) has the highest reported sensitivity, specificity and accuracy to evaluate the N0 neck,[18,19] but this strategy has not yet been adopted widely.[20-24] In our patients with T1 oral cavity squamous cell carcinoma, the 10% (8 out of 77) risk of having occult lymph node metastases was well below the 20% cutoff point for elective surgical treatment of the cN0 neck, as proposed by Weiss et al.[7] Based on these findings alone there seems no indication to perform SND I-III on patients whose US stage is cT1N0M0; of course, factors such as pernineural invasion, tumor depth and disease-specific survival should be taken into account as well before strong recommendations can be made. Future research will be focused on these specific characteristics. Contrastingly, the 29% (32 out of 112) risk in cT2N0M0 patients obviously demands elective surgical treatment of the neck, as do the 25% (5 out of 20) risk in T3 patients and the 33% (5 out of 15) risk in T4 patients.

Perioperative frozen section sampling had been performed in the majority of cases (184 out of the 224 patients: 75%), even in the absence of suspicious nodes. In this way, almost half of the necks that contained occult metastases (24 of 50) had been identified perioperatively. Neck dissection had been extended in 24 patients, mostly because frozen section sampling had revealed tumor-positive lymph nodes. In this additional part of each neck dissection specimen (levels IV and V) not a single metastatic node was found. There is an indication for postoperative radiotherapy when there are multiple lymph node metastases, or when there is extracapsular spread and probably also when only level III is affected (in this study: 2%, i.e. 5 out of the 224 patients). Several authors mentioned the importance of 'skip metastases'. Byers et al.[12] defined skip metastases as tumor-positive lymph nodes in level III or IV, while levels I and II were unaffected. They reported an incidence of 15.8%. When focused on the cN0 necks with histopathologically proven metastasic spread to level IV only, 5 out of the 34 patients remained. Thus, frequency of skip metastases solely to level IV was 2%. Percentages of sole metastases in level IV were also low in the studies by Crean et al.[13] and Shah et al.[9]: 4% and 1.5%, respectively. Preoperative US evaluation of the neck had not been used in two of the studies, but if it had, some of the metastases might have been found, which would have lowered these percentages even further. When US evaluation revealed cT2-4N0 oral cavity squamous cell carcinoma, standard SND I-III with sampling of levels I, II and III appeared to focus on the appropriate levels at risk. There were no indications to include level IV. Routine perioperative frozen section sampling was not indicated either, because a single tumor-positive node in level I or level II did not seem to justify extension of the neck dissection to MRND. When histopathological evaluation revealed multiple metastases or extracapsular spread, postoperative radiotherapy was indicated, in line with the Dutch guideline[25] and the international standards.

When we considered the size of the metastatic deposits in the 44 documented pN+ necks, 77% (n=34) fell into the smallest diameter category of 0-5 mm. Therefore, we believe that our preoperative approach consisting of palpation and US (+/- FNAC) represents the upper accuracy limits of the currently available minimally invasive preoperative staging techniques. Recently, sentinel lymph node biopsy (SLNB) and fluoro-deoxy-glucose positron emission tomography (FDG-PET) have been introduced as diagnostic options to reduce the risk of occult metastases to less than 20%. Most of the SLNB research consisted of pilot studies in which fairly promising results were found. Paleri et al.[26] conducted a meta-analysis on 19 articles that evaluated the use of SLNB in oral and oropharyngeal cancer. They concluded that although none of these pilot studies were blinded, SLNB showed high sensitivity in oral and oropharyngeal squamous cell carcinoma and the results were reliable and reproducible. However, the localisation of the lymph nodes played an important role: nodes in level I were more difficult to examine by US and SLNB than nodes in other levels[6,27]. When we addressed this issue in our 50 pN+ necks, we found sole tumor-positive nodes in level I in 13 cases (26%). One of the metastatic deposits had a smallest diameter of 6-10 mm, whereas all the other 12 deposits fell into the 0-5 mm category (92% of the metastases in level I). Especially the floor of mouth tumors had a tendency to affect level I (10 out of 21; 48%). These findings imply that the ultimate preoperative technique will have to be able to detect micrometastatic deposits and correctly stage the lymph nodes in level I.

No consensus has been reached about the use of FDG-PET to stage the cN0-neck. A former study conducted at our centre[28] showed that FDG-PET had remarkably low sensitivity in patients whose neck had been staged cN0 by palpation and US (+/- FNAC). This was in line with the results of other studies after correction for the preoperative neck status. The sizes of the metastatic deposits in the current study were comparable with those in our former study. Therefore, 77% of the metastases would have been hard to diagnose with FDG-PET, because their smallest diameter was less than 5 mm. This indicates that FDG-PET is unlikely to play a future role in the preoperative detection of occult metastatic deposits. Level I nodes would be especially difficult to display and diagnose, due to overprojection of the primary tumor.

At present histopathological staging of the neck seems to be superior to any type of noninvasive preoperative staging technique. However, promising results have recently been published on the detection of micrometastases in prostate cancer using new MRI contrast agents (ultrasmall super-paramagnetic iron oxide [USPIO])[29]. Until now, very few results are available in patients with head and neck squamous cell carcinoma, but the approach seems promising with a sensitivity of 86-96% and a specificity of 77-100%[30-32]. To our knowledge, no studies have been published on oral cavity squamous cell carcinoma alone. At our centre, we are currently conducting a prospective pilot study on USPIO in patients with cN0 squamous cell carcinoma of the oral cavity.

Conclusions

In patients with cN0 squamous cell carcinoma of the oral cavity, the occult metastatic rate was 22% (50 out of the 224 patients) after a combination of palpation and US +/- ultrasound guided FNAC had been used to stage the neck. In the patients with cT1N0M0, the occult metastic rate was 10% (8 out of the 77 T1 patients), so routine SND I-III might not be necessary.

Selective neck dissection of level I-III remains the elective neck dissection of choice in cT2-4N0 cases. When frozen section sampling is tumor-positive, it does not seem to be necessary to extend routine perioperative frozen section sampling or neck dissection to levels IV and V, because no metastases were found beyond level III. Therefore the indications for routine perioperative frozen section sampling are limited.

Reference List

1. Leemans CR, Tiwari R, Nauta JJ, van der Waal, I, Snow GB. Regional lymph node involvement and its significance in the development of distant metastases in head and neck carcinoma. Cancer 1993; 71:452-456.
2. Leemans CR, Tiwari R, Nauta JJ, van der Waal, I, Snow GB. Recurrence at the primary site in head and neck cancer and the significance of neck lymph node metastases as a prognostic factor. Cancer 1994; 73:187-190.
3. Snow GB, Annyas AA, van Slooten EA, Bartelink H, Hart AA. Prognostic factors of neck node metastasis. Clin Otolaryngol 1982; 7:185-192.
4. Van den Brekel MW. Lymph node metastases: CT and MRI. Eur J Radiol 2000; 33:230-238.
5. Van den Brekel MW, Castelijns JA, Stel HV et al. Occult metastatic neck disease: detection with US and US-guided fine-needle aspiration cytology. Radiology 1991; 180:457-461.
6. Pitman KT, Ferlito A, Devaney KO, Shaha AR, Rinaldo A. Sentinel lymph node biopsy in head and neck cancer. Oral Oncol 2003; 39:343-349.
7. Weiss MH, Harrison LB, Isaacs RS. Use of decision analysis in planning a management strategy for the stage N0 neck. Arch Otolaryngol Head Neck Surg 1994; 120:699-702.
8. Crile G. Landmark article Dec 1, 1906: Excision of cancer of the head and neck. With special reference to the plan of dissection based on one hundred and thirty-two operations. By George Crile. JAMA 1987; 258:3286-3293.
9. Shah JP, Candela FC, Poddar AK. The patterns of cervical lymph node metastases from squamous carcinoma of the oral cavity. Cancer 1990; 66:109-113.
10. Spiro RH, Morgan GJ, Strong EW, Shah JP. Supraomohyoid neck dissection. Am J Surg 1996; 172:650-653.
11. Traynor SJ, Cohen JI, Gray J, Andersen PE, Everts EC. Selective neck dissection and the management of the node-positive neck. Am J Surg 1996; 172:654-657.
12. Byers RM, Weber RS, Andrews T, McGill D, Kare R, Wolf P. Frequency and therapeutic implications of “skip metastases” in the neck from squamous carcinoma of the oral tongue. Head Neck 1997; 19:14-19.
13. Crean SJ, Hoffman A, Potts J, Fardy MJ. Reduction of occult metastatic disease by extension of the supraomohyoid neck dissection to include level IV. Head Neck 2003; 25:758-762.
14. Sobin LH, Fleming ID. TNM Classification of Malignant Tumors, fifth edition (1997). Union Internationale Contre le Cancer and the American Joint Committee on Cancer. Cancer 1997; 80:1803-1804.
15. Medina JE, Byers RM. Supraomohyoid neck dissection: rationale, indications, and surgical technique. Head Neck 1989; 11:111-122.
16. Van den Hoogen FJ, Manni JJ. Value of the supraomohyoid neck dissection with frozen section analysis as a staging procedure in the clinically negative neck in squamous cell carcinoma of the oral cavity. Eur Arch Otorhinolaryngol 1992; 249:144-148.
17. Stern WB, Silver CE, Zeifer BA, Persky MS, Heller KS. Computed tomography of the clinically negative neck. Head Neck 1990; 12:109-113.

18. Van den Brekel MW, Castelijns JA, Stel HV, Golding RP, Meyer CJ, Snow GB. Modern imaging techniques and ultrasound-guided aspiration cytology for the assessment of neck node metastases: a prospective comparative study. Eur Arch Otorhinolaryngol 1993; 250:11-17.
19. Van den Brekel MW, Reitsma LC, Quak JJ et al. Sonographically guided aspiration cytology of neck nodes for selection of treatment and follow-up in patients with N0 head and neck cancer. AJNR Am J Neuroradiol 1999; 20:1727-1731.
20. Kowalski LP, Magrin J, Waksman G et al. Supraomohyoid neck dissection in the treatment of head and neck tumors. Survival results in 212 cases. Arch Otolaryngol Head Neck Surg 1993; 119:958-963.
21. Smith GI, O'Brien CJ, Clark J et al. Management of the neck in patients with T1 and T2 cancer in the mouth. Br J Oral Maxillofac Surg 2004; 42:494-500.
22. Byers RM, Clayman GL, McGill D et al. Selective neck dissections for squamous carcinoma of the upper aerodigestive tract: patterns of regional failure. Head Neck 1999; 21:499-505.
23. Dias FL, Lima RA, Kligerman J et al. Relevance of skip metastases for squamous cell carcinoma of the oral tongue and the floor of the mouth. Otolaryngol Head Neck Surg 2006; 134:460-465.
24. Results of a prospective trial on elective modified radical classical versus supraomohyoid neck dissection in the management of oral squamous carcinoma. Brazilian Head and Neck Cancer Study Group. Am J Surg 1998; 176:422-427.
25. Knegt PP, Keus RB, Roodenburg JL. [The practice guideline 'Carcinoma of the oral cavity and oropharynx']. Ned Tijdschr Geneeskd 2006; 150:83-88.
26. Paleri V, Rees G, Arullendran P, Shoaib T, Krishman S. Sentinel node biopsy in squamous cell cancer of the oral cavity and oral pharynx: a diagnostic meta-analysis. Head Neck 2005; 27:739-747.
27. Takes RP, Knegt P, Manni JJ et al. Regional metastasis in head and neck squamous cell carcinoma: revised value of US with US-guided FNAB. Radiology 1996; 198:819-823.
28. Wensing BM, Vogel WV, Marres HA et al. FDG-PET in the clinically negative neck in oral squamous cell carcinoma. Laryngoscope 2006; 116:809-813.
29. Heesakkers RA, Futterer JJ, Hovels AM et al. Prostate cancer evaluated with ferumoxtran-10-enhanced T2*-weighted MR Imaging at 1.5 and 3.0 T: early experience. Radiology 2006; 239:481-487.
30. Mack MG, Balzer JO, Straub R, Eichler K, Vogl TJ. Superparamagnetic iron oxideenhanced MR imaging of head and neck lymph nodes. Radiology 2002; 222:239-244.
31. Sigal R, Vogl T, Casselman J et al. Lymph node metastases from head and neck squamous cell carcinoma: MR imaging with ultrasmall superparamagnetic iron oxide particles (Sinerem MR) -- results of a phase-III multicenter clinical trial. Eur Radiol 2002; 12:1104-1113.
32. Curvo-Semedo L, Diniz M, Migueis J et al. USPIO-enhanced magnetic resonance imaging for nodal staging in patients with head and neck cancer. J Magn Reson Imaging 2006; 24:123-131.

CHAPTER 3.1

FDG-PET in the clinically negative neck in oral cavity carcinoma

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Abstract

Objective

With improved diagnostic imaging techniques it remains difficult to reduce occult metastatic disease in squamous cell carcinoma of the oral cavity (SCCOC) to less than 20%. Therefore supraomohyoid neck dissection (SOHND) still is a valuable staging procedure in these patients.

This study was conducted to see whether adding FDG-PET to routine preoperative workup could reduce the incidence of occult metastasis.

Methods

Patients with clinically and ultrasonographically staged cN0 SCC of the oral cavity underwent FDG-PET prior to SOHND. Histologic examination of neck dissection specimens was used as a 'gold standard'.

Results

Twenty-eight consecutive patients were included, representing 30 necks. Occult metastatic disease was found in 30% of SOHND specimens. Average diameter of metastatic deposits was 4.3 mm. Sensitivity, specificity and accuracy of FDG-PET was 33%, 76% and 63% respectively.

Conclusions

In patients with cN0 SCC of the oral cavity FDG-PET does not contribute to the preoperative work-up. FDG-PET does not replace SOHND as a staging procedure.

Introduction

The oral cavity is one of the cancer sites in the the head and neck accompanied by a high incidence of occult regional metastasis. As the presence of cervical lymph node metastasis significantly reduces survival, this important prognostic factor remains an issue for scientific debate. In these discussions the changing necessity, diagnostic value and therapeutic role of a selective neck dissection of levels I-III, also called supraomohyoid neck dissection (SOHND), is often addressed.

In 1980, Hanley[1] summarizes the opinion at that time about SOHND as a well-recognized, although generally unaccepted form of treatment in oral cavity cancer patients. He compared the SOHND to the standard radical neck dissection in 62 patients with oral cavity tumors and found "similar and no worse results for the SOHND". He felt that less than radical neck dissection required further exploration. Since then the opinion about SOHND has gradually changed[2]. The SOHND has been popularized over the years and has become a generally accepted staging procedure for the clinically negative neck in oral cancer patients[3,4]. In cases of limited nodal disease on histopathological examination some consider it therapeutic[5]. Several studies have shown that even with improved diagnostic imaging techniques it still remains difficult to reduce occult metastatic disease in oral cavity cancer to less than in 20% of the patients[3,4]. The 20% threshold is considered important as elective treatment of the neck remains indicated when the probability of occult neck metastases exceeds 20%[6].

Palpation of the neck, with a sensitivity and specificity of 60-80%, is not a very accurate way to search for cervical metastases. Computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography (US), sentinel lymph node biopsy (SLNB) and ultrasound-guided fine needle aspiration cytology (USgFNAC) have shown to be superior to palpation, with the latter being the most accurate way of investigation. However in patients with a clinically negative neck even USgFNAC is reported to have a sensitivity of no more than 48-76%, most likely explained by the limited tumorload[7,8]. USgFNAC of the sentinel node does not seem to increase sensitivity[9]. With these results in mind the risk of occult metastatic disease remains between 15-25%[9,10].

Positron emission tomography (PET) with fluorodeoxyglucose (FDG) is increasingly used in preoperative staging of cancer patients. FDG depicts the increased metabolism of malignant cells as compared to normal cells. Reports on the value of FDG-PET in detecting occult metastatic disease have been contradictionary with a reported sensitivity ranging from 0-100% and specificity from 92-100%[11-13]. The added value of FDG-PET to the clinical and ultrasonographical evaluation of the neck in oral carcinoma has not been properly investigated. We conducted a study in order to evaluate whether further reduction of occult metastatic disease in oral carcinoma can be achieved by adding FDG-PET scanning to the preoperative work-up. With 21% reported occult metastatic disease in oral carcinoma after a negative ultrasonographic investigation in our hospital[10] this could implicate that a diagnostic SOHND would no longer be indicated.

Materials and Methods

Patients

This prospective study was performed at the Radboud University Nijmegen Medical Centre between June 2001 and December 2003. All patients planned for SOHND as part of the treatment for a clinically N0 (cN0) squamous cell carcinoma (SCC) of the oral cavity were included in the study and offered a FDG-PET-scan. Prior to inclusion all patients were clinically staged N0. A cN0 neck is defined as a neck staged N0 by preoperative palpation by an experienced ENT- surgeon, oral and maxillofacial surgeon and radiotherapist and a standard preoperative US performed with USgFNAC on indication. FNAC of enlarged lymphnodes was performed in nodes with a diameter >0.5 cm. In case of a cN+ neck, the patient was offered a modified radical neck dissection (MRND) and was excluded from the study.

The study was approved by the local Medical Ethics Committee. Informed consent was obtained from all patients. No patient suffered from cancer within 5 years prior to this study nor was previously treated by radiotherapy or chemotherapy.

FDG-PET

A dedicated PET-scanner (ECAT-EXACT, Siemens/CTI, Knoxville, TN, USA) was used for data acquisition. Prior to FDG-injection, patients were fasting for at least 6 hours. Intake of sugar-free liquids was permitted. Immediately prior to the procedure, the patients were hydrated with 500 ml of water. One hour after intravenous injection of 220-250 MBq FDG (Mallinckrodt Medical, Petten, The Netherlands) and 20 mg furosemide, emission and transmission images of the head and neck area were acquired (2-3 bedpositions, 10 minutes per bedposition). The images were corrected for attenuation and reconstructed using the ordered-subsets expectation maximization (OSEM) algorithm. The reconstructed images were displayed in coronal, transverse and sagittal planes and evaluated by three nuclear medicine physicians.

The mean glucose level just before PET-imaging was 5.3 mmol/L; three patients had diabetes mellitus (glucose levels 10.3, 6.8 and 3.4 mmol/L).

For statistical analysis the sensitivity, specificity and accuracy of FDG-PET were calculated.

Surgical Technique and Pathologic Examination

SOHND was performed as described by Medina et al[2]. In case of enlarged or suspicious nodes found during surgery, frozen stage section (FSS) analysis was performed. If positive, the neck dissection was extended to a MRND. The neck dissection specimen was marked anatomically by the surgeon (a senior staff-member of the department of Otorhinolaryngology and Head & Neck Surgery or of the department of Oral and Maxillofacial Surgery) and sent for pathologic examination consisting of node count, evaluation of malignancy in any of the nodes and extracapsular spread. Standard sectioning and HE-staining was performed on all lymph nodes. Lymph node metastases were defined as micrometastasis when a metastatic deposit had a largest diameter of less then 4 mm.

Results

Thirty patients (15 male, 15 female; median age 60 years, range 32 - 84 years) were enrolled. One FDG-PET-scan was unevaluable due to significant movement of the (diabetic) patient during imaging. One patient had a SOHND 49 days after FDG-PET and was also excluded. Twenty-eight scans could be evaluated (15 women, 13 men), representing 30 SOHNDs. Site of the primary tumor and T-stage are shown in ***table 1***.

	n	T1	T2	T3	T4
Floor of the Mouth	9	3	4	1*	1*
Tongue	17	6	8	3	0
Alveolar Proces	2	0	1	0	1

Table 1: Localizations and clinical T-stage of the 28 tumors
* = medial floor of the mouth

None of the patients had any sign of metastatic spread based on clinical examination and US of the neck. In 8 patients, US was supplemented with USgFNAC, which resulted in negative cytology. Additionally, 4 patients had a CT of the head and neck, all without suspect nodes. In 26 patients (28 necks) FSS of the neck specimen was performed: 25 (89%) necks were negative and 3 (11%) were positive. All 3 necks positive on FSS turned out to be true-positive and one of 25 negative FSS specimens turned false negative during further pathologic investigation. In the 3 necks (10% of necks) with a positive FSS of the SOHND-specimen, the SOHND was extended to a MRND. No additional metastatic nodes were found in levels IV and V. A total number of 555 nodes was examined in 28 patients. The total number of nodes found in regions I to III varied from 11 to 38. Nine out of 30 necks (30%) contained occult metastases in a total of 16 lymphnodes; no bilateral metastases were found.
The average diameter of the metastatic deposit was 4.3 mm (range 0.5 mm to 8.0 mm). Five of the malignant nodes showed signs of extracapsular spread, being a prognostic factor of enhanced metastatic spread[3]. An overview of the patients and their nodes, is presented in ***table 2*** **(addendum).**

USgFNAC

Three of 8 patients (38%; 3 of 9 punctured necks: 33%) in whom USgFNAC was negative, did have lymph node metastases at pathological examination of the SOHND specimen: in one case a node in the punctured level was positive; the other two patients had one and two positive nodes in non-punctured levels. In patients in whom no USgFNAC was performed, 6 of 21 SOHND specimens proved to be positive for lymph node metastases (29%).

FDG-PET

In 1 patient (3,6%) the FDG-PET-scan showed no sign of the primary tumor as this tumor (tongue) was already removed by a radical excision biopsy in a secondary referral center. The other 27 primary tumorsites were correctly depicted. This leads to a sensitivity of 100% for visualizing the primary tumor.

In 8 cases (29%) FDG-PET showed ipsilateral hot-spots suspect for possible metastases; 20 scans representing 22 necks were negative. Patients were on average surgically treated within 14 days (1-30, median 12 days) after receiving their PET-scan. Twenty-eight patients underwent 30 neck dissections (2 bilateral, due to a floor of the mouth tumor crossing the midline).

FDG-PET correctly recognized 3 out of 9 (33%) afterwards pathologically proven positive necks; these positive nodes were found in the correctly depicted level, although one patient had 7 positive nodes divided among levels I and II. His PET-scan only showed 3 positive spots in level II. In 5 patients FDG-PET showed a suspect node which was not confirmed by pathologic examination; in one of these cases USgFNAC was performed 3 weeks prior to FDG-PET. FDG-PET also failed to show any positive nodes in 6 patients whilst pathologically present, leading to a sensitivity and specificity of 33% and 76% respectively for 30 necks. Accuracy reached 63% for FDG-PET. If SOHND would only be performed when FDG-PET was positive for lymph nodes, the number of SOHNDs would have been reduced by 73% (from 30 to 8). However, this algorythm would result in 6 out of 30 necks with unrecognized occult metastases (20%).

Discussion

Supraomohyoid neck dissection has shown to be a valid staging procedure in cN0 oral SCC[3]. CT, MRI and US lack sensitivity and specificity for diagnosing occult metastatic disease as micrometastases can occur in the absence of morphologic changes in lymph nodes, while these changes can be both reactive and metastatic. That is the main reason why USgFNAC is considered to be superior to these imaging modalities, especially when normal-sized and thus non-suspicious nodes in the first echelons are punctured. As the majority of patients in this study did not receive FNAC, this might explain why the 30% of necks with occult metastatic nodes in this study was higher than the initially reported 21%[10] from our institute. All metastases in the SOHND-specimens were located in the first echelons. As the metastatic parts of the affected nodes were very small, morphologic changes were unlikely to appear in the majority. Furthermore, CT-scanning of the head and neck is no standard preoperative staging technique in patients with a cN0-neck in oral SCC according to the national Dutch guideline on diagnosis and treatment of oral and oropharyngeal cancer.

Several studies have shown that it is possible to reduce occult metastatic disease in oral SCC to approximately 20%[5,10]. As a 20% false-negative rate is considered to be the limit for a wait and see policy versus elective treatment of the neck[6], clinicians are expected to be divided into two groups advocating either one of these treatment strategies. Many surgeons feel that the morbidity of a SOHND is acceptably low and outweighs the risk of being confronted with advanced neck disease after a wait and see or wait and scan policy[14]. Nevertheless, if a diagnostic strategy would further reduce the rate of occult metastasis, SOHND could be abandoned. Recent studies have mainly focused on sentinel node biopsy and FDG-PET scanning of the neck.

SLNB might possibly identify those patients that harbour occult metastatic disease in cN0 oral SCC. Ross et al.[15] describe the preliminary results of a multicenter trial in patients with T1-2N0 oral cavity/oropharynx carcinoma. In 93% of 134 cases a sentinel node could be identified. In 55 cases SLNB was combined with an elective neck dissection. Occult metastatic disease was present in 34%. Sensitivity of this technique was reported to be 93% in all oral SCC. In floor of the mouth SCC only however identification of the SLN was possible in 86% (n=43) and sensitivity reached 80%. Beside selection of patients for (additional) neck surgery, histopathologic evaluation of the sentinel node might limit cost and time consuming pathological evaluation by performing step serial sectioning and immunohistochemistry of the sentinel nodes which are most suspected to harbour metastases.

However, skip metastases might prove to be a problem[16]. Difficulties identifying level I sentinel lymph nodes in oral SCC have been reported[15]. In our series, 31% of the metastatic nodes were located in level I. Thus, questions wether SLNB offers a significant advantage over SOHND still remain. Unresolved issues regarding this technique are the feasability of and efficacy in multiple level sentinel nodes and the cost-effectiveness.

Furthermore, underestimation of occult metastatic disease with standard sectioning and HE staining is likely to be present in about 8%[17,18]. It is unclear if these micrometastases need more than a SOHND or if SOHND can be considered adequate treatment in these cases. Potential overtreatment of such limited disease with a MRND needs to be subject of clinical studies as stated by Pitman et al. in a review on SLNB in head and neck cancer[19]. Nieuwenhuis et al.[9] investigated the role of USgFNAC of the sentinel node in cT1-2N0 oral/oropharyngeal carcinoma. Although the sentinel node could be identified and aspirated in 38 out of 39 patients, it did not decrease false negative rate compared to USgFNAC alone. The additional value of sentinel node cytology was thus questioned. Considerable attention has been paid to FDG-PET in the evaluation of the N0 neck in head and neck cancer. In our study we have included only patients without evidence of metastatic neck disease in preoperative evaluation consisting of at least palpation and US and who were thus scheduled for a surgical treatment including a SOHND. Sensitivity in this selected patient group is insufficient to refrain from SOHND on the basis of FDG-PET.

In FDG-PET studies specifically addressing oral cavity or oropharyngeal cancer patients with a cN0 neck huge variations in sensitivity (from 0 to 100%) are reported[11-13, 20]. Brouwer et al.[11] showed that in the studies using routine histopathological work-up[11,12] a much higher sensitivity (67%-100%) for the detection of occult lymph node metastases was found in comparison to the studies in which step sectioning and immunohistochemistry as part of the sentinel node procedure was performed. In the latter studies a sensitivity of only 0-40% was found[13,20]. They point out that the histopathological method used seems to be the most important factor for the differences in sensitivity. However, we feel that patient selection and differences in inclusion criteria are other major reasons for these differences. In the “less sensitive studies” only patients were included who were clinically as well as ultrasonographically N0 and in the “sensitive studies” patients were included that had a clinically negative neck but often had radiological evidence of metastatic disease[12-14,20]. If the results of the studies in ***table 3*** are combined, while excluding patients with radiological evidence of metastases, overall sensitivity drops from 38% to 25% (84 patients, 92 necks). This is in line of the diagnostic yield of FDG-PET in our study of patients with lymph node metastases all smaller than 8 mm.

	# patients in study	# patients palpably N0	# patients palpably and radiographically N0		Pathology	Sensitivity PET in study	Specificity PET in study	Accuracy PET in study
			Pat.	Necks				
Myers et al.[12] 1998	14	14	8	12	?	78%	100%	92%
Civantos et al.[20] 2001	18	18	18	18?	IHSN†	30%	100%	61%
Hyde et al.[13] 2003	19	18	18	20	IHSN	0%	100%	78%
Brouwer et al.[11] 2003	15	15	12	12	HE	67%	92%	87%
Wensing et al. 2005	28	28	28	30	HE	33%	76%	63%
Total	94	93	84	92	-	38%	92%	74%
Corrected data for 84 patients palpably and radiographically N0						25%‡	91%	72%

Table 3: Comparison of studies considering the use of FDG-PET to find metastatic spread in patients suffering from head and neck carcinoma (laryngeal and hypopharyngeal cancer excluded) regarding the clinically N0-neck.
* HE = Haematoxylin Eosin staining
? = could not be retrieved from study
† IHSN = ImmunoHistochemistry of Sentinel Node only
‡ corrected percentages are based on number of treated necks (108 – 4 of Braams et al. since no sensitivity could be estimated in the 2 remaining patients)

Conclusions

In conclusion, FDG-PET does not lower the false-negative rate of occult lymph node metastases in patients with an oral SCC and a clinically and US negative neck below the clinically required 20% of patients. Therefore, FDG-PET has no added value in the preoperative work-up. FDG-PET alone or in combination with US (+/- FNAC) cannot replace SOHND as a staging procedure.

Pt-#	Age	M/F	cT-stage	US / FNAC	FDG-PET	PATH†	Diameter of metastatic deposit
1	76	F	T4	Neg / np*	Neg	Neg	-
2	79	F	T2	Neg / Neg	Neg	Neg	-
3	55	F	T1	Neg / np	Neg	Neg	-
4 a	55	F	T4	Neg / Neg	Neg	Neg	-
4 b	55	F	T4	Neg / Neg	Neg	Neg	-
5	71	F	T2	Neg / np	Neg	Neg	-
6	58	F	T2	Neg / np	Neg	1 in I	2 mm
7	55	M	T2	Neg / Neg	Pos, 2 in II	Neg	-
8	30	M	T2	Neg / np	Pos, 1 in II	Neg	-
9	66	F	T1	Neg / np	Neg	Neg	-
10	77	F	T2	Neg / np	Neg	Neg	-
11	79	M	T2	Neg / np	Neg	Neg	-
12	47	M	T1	Neg / np	Neg	1 in I	5 mm
13	58	F	T3	Neg / np	Neg	Neg	-
14	82	F	T2	Neg / np	Pos, 1 in II	1 in II	1 mm
15	53	M	T1	Neg / Neg	Neg	1 in I	2 mm
16	52	M	T3	Neg / np	Pos, 1 in II	Neg	-
17	44	F	T2	Neg / Neg	Neg	2 in II	4 and 2 mm
18	50	M	T1	Neg / np	Pos, 1 in II	1 in II	7 mm
19	64	M	T1	Neg / Neg	Neg	Neg	-
20	71	F	T2	Neg / np	Pos, 1 in II	Neg	-
21	45	M	T1	Neg / Neg	Neg	Neg	-
22	59	F	T2	Neg / np	Pos, 2 in II	Neg	-
23	47	M	T1	Neg / np	Neg	Neg	-
24	55	M	T3	Neg / np	Neg	Neg	-
25	66	M	T1	Neg / np	Neg	Neg	-
26	72	F	T2	Neg / np	Pos, 3 in II	6 in II, 1 in I	3 x 8, 7, 5, 4 & 1,2 mm
27	42	M	T2	Neg / Neg	Neg	1 in II	4 mm
28 a	70	F	T3	Neg / np	Neg	1 in I	5 mm
28 b	70	F	T3	Neg / np	Neg	Neg	-

Table 2. Demographic, clinical, imaging and pathological characteristics of the 28 patients. All nodes were found on the side of the tumor. * np = not performed. † PATH = pathological examination: number of metastatic nodes in level

CHAPTER 3.1

Reference list

1. Hanley DJ. Supraomohyoid neck dissection. Br J Plast Surg. 1980;33:136-7.
2. Medina JE, Byers RM. Supraomohyoid neck dissection: rationale, indications, and surgical technique. Head and Neck 1989;11:111-22.
3. Brazilian Head and Neck Cancer Study Group.Results of a prospective trial on elective modified radical classical versus supraomohyoid neck dissection in the management of oral squamous carcinoma. Am J Surg 1998;176:422-7.
4. Shah JP. Patterns of cervical lymph node metastasis from squamous carcinomas of the upper aerodigestive tract. Am J Surg 1990;160:405-9.
5. Kerrebijn JD, Freeman JL, Irish JC et al. Supraomohyoid neck dissection. Is it diagnostic or therapeutic? Head and Neck 1999;21:39-42.
6. Weiss MH, Harrison LB, Isaacs RS. Use of decision analysis in planning a management strategy for the stage N0 neck. Arch Otolaryngol Head Neck Surg 1994;120:699-702.
7. van den Brekel MW, Castelijns JA, Stel HV et al. Occult metastatic neck disease: detection with US and US-guided fine-needle aspiration cytology. Radiology 1992;180:457-61.
8. Takes RP, Righi PD, Meeuwis CA et al. The value of ultrasound with ultrasound-guided fine-needle aspiration biopsy compared to computed tomography in the detection of regional metastases in the clinically negative neck. Int J Radiat Oncol Biol Phys 1998;40:1027-32.
9. Nieuwenhuis EJ, Castelijns JA, Pijpers R et al. Wait-and-see policy for the N0 neck in early-stage oral and oropharyngeal squamous cell carcinoma using ultrasonography-guided cytology: is there a role for identification of the sentinel node? Head and Neck 2002;24:282-9.
10. van den Hoogen FJA, Westerbeek BC, Joosten FB, Bruaset I, Marres HA. Supraomohyoid neck dissection in the ultrasonographically and clinically negative neck in oral carcinoma. Clin Otolaryngol 2001;26:340.
11. Brouwer J, de Bree R, Comans EF, Castelijns JA, Hoekstra OS, Leemans CR. Positron emission tomography using [(18)F]fluorodeoxyglucose (FDG-PET) in the clinically negative neck: is it likely to be superior? Eur Arch Otorhinolaryngol 2004;261(8):479-83.
12. Myers LL, Wax MK. Positron emission tomography in the evaluation of the negative neck in patients with oral cavity cancer. J Otolaryngol 1998;27:342-7.
13. Hyde NC, Prvulovich E, Newman L, Waddington WA, Visvikis D, Ell P. A new approach to pre-treatment assessment of the N0 neck in oral squamous cell carcinoma: the role of sentinel node biopsy and positron emission tomography. Oral Oncol 2003;39(4):350-60.
14. Andersen PE, Cambronero E, Shaha AR, Shah JP. The extent of neck disease after regional failure during observation of the N0 neck. Am J Surg 1996;172:689-91.
15. Ross GL, Soutar DS, MacDonald GD et al. Sentinel node biopsy in head and neck cancer: preliminary results of a multicenter trial. Ann Surg Oncol 2004;11:690-6.
16. Ferlito A, Shaha AR, Rinaldo A, Pellitteri PK, Mondin V, Byers RM. "Skip metastases" from head and neck cancers. Acta Otolaryngol 2002;22:788-91.

17. Ambrosch P, Brinck U. Detection of nodal micrometastases in head and neck cancer by serial sectioning and immunostaining. Oncology (Huntingt) 1996;10:1226-9.
18. Woolgar JA. Micrometastasis in oral/oropharyngeal squamous cell carcinoma: incidence, histopathological features and clinical implications. Br J Oral Maxillofacial Surg 1999;37:181-6.
19. Pitman KT, Ferlito A, Devaney KO, Shaha AR, Rinaldo A. Sentinel lymph node biopsy in head and neck cancer. Oral Oncol 2003;39(4):343-9.
20. Civantos FJ, Gomez C, Duque C et al. Sentinel node biopsy in oral cavity cancer: correlation with PET scan and immunohistochemistry. Head and Neck 2003;25(1):1-9.

CHAPTER 3.2

Optimised PET reconstruction in the head and neck area: improved diagnostic accuracy

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Abstract

Objective

Reconstruction parameters are an important factor in PET image quality. In the head and neck Area, where the level of photon attenuation is relatively low, standard whole-body reconstruction (SWR) parameters may lead to suboptimal results. The purpose of this study was to evaluate the impact of optimised head and neck reconstruction (OHR) parameters on image quality and diagnostic accuracy, using pathology as the gold standard.

Methods

SWR parameters consisted of 2 iterations, 8 subsets and a 6-mm Gaussian filter. Predetermined OHR parameters were 4 iterations, 16 subsets and a 5-mm Gaussian filter, generating images with increased spatial and contrast resolution but also with increased noise. SWR- and OHRbased FDG-PET images of 28 patients with malignancies in the head and neck area were evaluated for primary tumour and pathological lymph nodes. Diagnostic accuracy was determined by histopathological verification after lymph node dissection.

Results

Using OHR, sensitivity for detection of a primary tumour increased from 92% to 100%. Eleven additional lymph nodes were visualised in eight patients, resulting in an increased sensitivity for lymph node metastases from 11% to 44%. Specificity decreased from 89% to 74% owing to visualisation of small reactive lymph nodes. In total, using OHR, FDG-PET diagnosis improved in six patients (21%) at the expense of three additional false positives for lymph node metastasis (11%). Primary tumour SUV_{max} increased by 42%, indicating enhanced contrast resolution.

Conclusions

Image reconstruction adapted to low photon attenuation in the head and neck area may improve image quality and the diagnostic value of FDG-PET, despite a slightly higher false positive rate attributable to the fact that visualisation of FDG accumulation in benign reactive lymph nodes is also enhanced.

Introduction

Primary tumours in the head and neck area are often small at the time of discovery, especially when located in the oral cavity. Lymph node metastases tend to be small and multiple in number. Among patients without clinically apparent lymph node metastasis (staged cN0), pathological examination after lymph node dissection shows occult metastases in up to 40%[1]. Accurate staging of the primary tumour and lymph nodes is essential for determination of prognosis and appropriate selection of therapeutic strategies.

Positron emission tomography with 18F-fluorodeoxyglucose (FDG-PET) provides high contrast resolution and high sensitivity for the detection and staging of a wide variety of malignant diseases. In the head and neck area, some authors have reported a high accuracy of FDG-PET for the detection of primary tumours and lymph node metastases[2-5]. However, others have reported a low sensitivity for the detection of lymph node metastases, especially micrometastases[6].

A major drawback of FDG-PET is its relatively limited image quality, expressed in a low spatial resolution and a tendency to produce noisy images. In PET scanning, image quality can be influenced by parameters such as injected dose, acquisition mode and acquisition times. Furthermore, it is reduced by physical limitations, such as annihilation photon non-collinearity, off-axis detector penetration, Compton scatter and positron range in tissue[7, 8]. Patient motion may also play a role in adversely affecting image quality.

An additional important factor that impacts on image quality is the image reconstruction procedure. The choice of an image reconstruction algorithm and its parameters affect contrast resolution, spatial resolution and level of noise. All three factors influence the measured standardised uptake values (SUVs) and clinical reporting[9]. Optimum values depend mainly on scanner characteristics and the level of attenuation. Specifically in the head and neck area, attenuation is much lower as compared to the central body. This results in better count statistics and lower noise levels by default. Less filtering is needed and more iterations may be used without creating unacceptable noise. Standard whole-body reconstruction (SWR) parameters, however, are optimised for the patient as a whole, and disregard particular issues relating to specific body parts such as the head and neck area.

The actual diagnostic benefit of optimised reconstruction algorithms for the head and neck area remains unconfirmed. The aim of this study was to assess the impact of better image quality from optimised head and neck reconstruction (OHR) images on diagnostic yield in the staging of malignancies in the head and neck area.

Materials and methods

Twenty-eight patients with newly diagnosed malignancies in the oral cavity were included (***table 1***). None of the patients had clinical signs of lymph node metastases, and none had evidence of lymph node metastases on ultrasonographic evaluation of the neck, including fine-needle aspiration of visible lymph nodes when appropriate. None of the patients had a history of diabetes mellitus, and fasting glucose levels were within the normal range.

Patients			**Tumour characteristics at pathology**	
No.	**Sex**	**Age**	**Tumour location**	**Primary tumor stage**
1	F	76	Left side of the tongue	**T4**
2	F	79	Right side of the tongue	**T2**
3	F	55	Right floor of the mouth	**T1**
4	F	55	Ventral floor of the mouth	**T4**
5	F	71	Right floor of the mouth	**T2**
6	F	58	Ventral floor of the mouth	**T2**
7	M	55	Right floor of the mouth	**T2**
8	M	30	Left side of the tongue	**T2**
9	F	66	Left side of the tongue	**T1**
10	F	77	Left side of the tongue	**T2**
11	M	79	Ventral floor of the mouth	**T2**
12	M	47	Ventral floor of the mouth	**T1**
13	F	58	Left side of the tongue	**T3**
14	F	82	Right side of the tongue	**T2**
15	M	53	Right side of the tongue	**T1**
16	M	52	Right side of the tongue	**T3**
17	M	20	Right side of the tongue	**T1**
18	M	64	Ventral floor of the mouth	**T1**
19	F	71	Left side of the tongue	**T2**
20	M	45	Left side of the tongue	**T1**
21	F	59	Right side of the tongue	**T2**
22	M	47	Right side of the tongue	**T1**
23	M	55	Left side of the tongue	**T3**
24	M	66	Left side of the tongue (EB)	**T1**
25	F	72	Left retromolar trigone	**T2**
26	M	79	Right side of the tongue	**T3**
27	M	42	Right side of the tongue	**T2**
28	F	70	Right side of the tongue	**T3**
Avg		**61**		

Table 1: Characteristics of patients included in the study

FDG-PET

All PET scans were acquired using a full-ring dedicated PET scanner (Siemens ECAT Exact 47, Siemens AG, Germany), with a voxel size of 5.15 mm in all directions. One hour after injection of 250 MBq FDG (Tyco-Mallinckrodt, Petten, The Netherlands), emission images were acquired in 3D mode. GE-based transmission imaging was performed for attenuation correction. Acquisition time per bed position was 5 min for emission and 3 min for transmission.

Image reconstruction

All PET scans were reconstructed using an iterative 2D ordered subset expectation maximisation (OSEM) algorithm[10]. For SWR, parameters were left unchanged for normal whole-body imaging (i.e. 2 iterations, 8 subsets and a three-dimensional Gaussian filter of 6 mm). Attenuation correction was based on segmented transmission images. Average reconstruction processing time for a whole body study was 3 minutes.
In addition, the head and neck area was reconstructed a second time using the OHR parameters. These parameters were determined beforehand, by three observers who reached a consensus in visual analysis of multiple reconstructions. The best results in respect of spatial resolution, contrast resolution, noise level, blurring and observer confidence were achieved on our system when using 4 iterations, 16 subsets and a three-dimensional Gaussian filter of 5 mm. Attenuation correction was based on non-segmented transmission images. With these settings, the average calculation time for two bed positions was 10 min. Examples of FDG-PET scans of the head and neck area generated with different reconstruction parameters are shown in ***figure 1***. In contrast, these values were clearly not suitable for the central body, as illustrated in ***figure 2***.

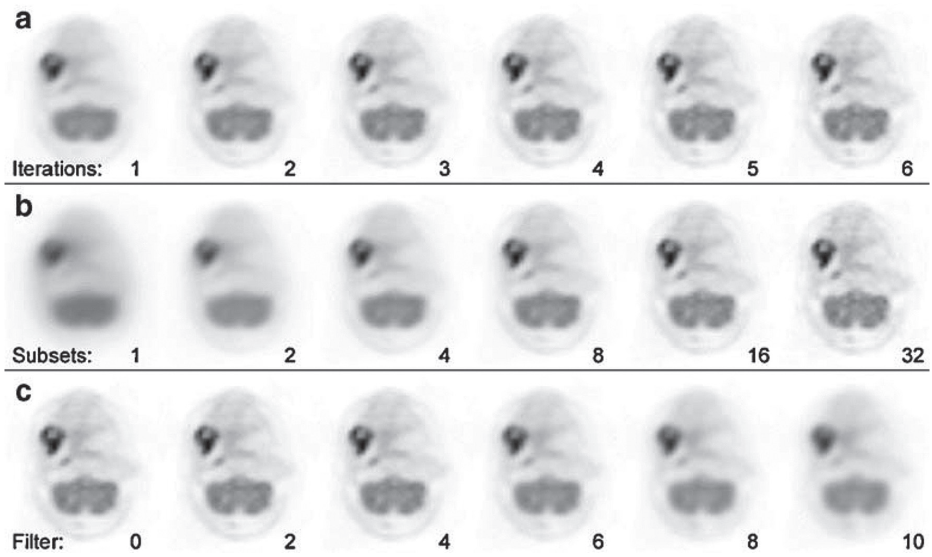

Figure 1: Effects of different reconstruction parameters on image quality. From left to right, reconstructions with a an increasing number of iterations, using fixed subsets (16) and no filter; b an increasing number of subsets, with fixed iterations (4) and no filter; and c an increasing Gaussian filter size, with fixed iterations (4) and subsets (16). Note the changes in visibility of the small lymph node in the dorsal nasopharyngeal wall, as well as better contour detection of the primary tumour

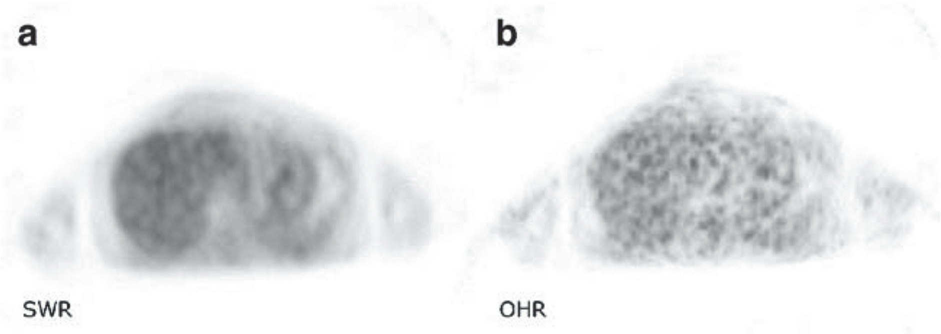

Figure 2: The effects of reconstruction optimised for low attenuation levels on image quality in more attenuated parts of the body. A transverse slice of a normal upper abdomen at the level of the liver and stomach is shown. **a:** Normal SWR images. **b:** Images reconstructed with the OHR parameters. The increase in noise level makes the images uninterpretable

Image analysis

All SWR- and OHR-reconstructed FDG-PET images were read independently by two experienced nuclear medicine physicians blinded to the final histopathological diagnosis. Differences between readers were settled by consensus. The visualisation, location and additional properties of the primary tumour and the number and location of lesions suspected to represent lymph node metastases were evaluated.

Histopathological verification

After FDG-PET, all patients but one underwent resection of the primary tumour and supra-omohyoidal lymph node dissection of the neck within 30 days (average 14 days), providing pathological findings as a gold standard. Patient 26 underwent neck dissection 49 days after FDG-PET. The neck dissection specimens were subjected to standard histopathological examination. All lymph nodes were examined by standard sectioning and haematoxylin and eosin staining.Using the outcome of histopathological staging, the sensitivity, specificity and predictive values for the detection of lymph node metastases by FDG-PETwere calculated for both the SWR and the OHR algorithm.

Results

A summary of the imaging results as compared with histological diagnosis is shown in ***table 2***. Subjectively, the OHR images were easier to read. The moderately higher noise level was outweighed by improved spatial resolution and recognition of details in both normal tissue and pathological lesions. Overall, the reviewers judged the OHR images to be of better quality and expressed a higher confidence in the reading.

	Primary tumour		Lymph node metastases			
	SWR	OHR	SWR	OHR	Nodal stage	Nodes (diameter)
1	+	+	0	0	pN0	0
2	+	+	0	0	pN0	0
3	+	+	0	0	pN0	0
4	+	+	0	0	pN0	0
5	+	+	0	0	pN0	0
6	+	+	0	0	pN1	1 (2mm)
7	+	+	0	3	pN0	0
8	+	+	0	1	pN0	0
9	+	+	0	0	pN0	0
10	+	+	0	0	pN0	0
11	+	+	0	0	pN0	0
12	-	+	0	0	pN1	1 (5 mm)
13	+	+	0	0	pN0	0
14	+	+	0	1	pN1	1 (2 mm)
15	+	+	0	0	pN1	1 (2 mm)
16	+	+	1	1	pN0	0
17	+	+	0	1	pN1	1 (7 mm)
18	+	+	0	0	pN0	0
19	+	+	0	1	pN0	0
20	-	+	0	0	pN0	0
21	+	+	1	2	pN0	0
22	+	+	0	0	pN0	0
23	+	+	0	0	pN0	0
24	-	-	0	0	pN0	0
25	+	+	1	3	pN2b	7 (1-8 mm)
26	+	+	0	1	pN2b	5 (3-5 mm)
27	+	+	0	0	pN1	1 (4 mm)
28	+	+	0	0	pN1	1 (5 mm)

Table 2: The number of primary tumours and pathological lymph nodes visualised with FDG PET on SWR images and OHR images. The final nodal stage was provided by histopathological examination

Primary tumours

In one patient, who had undergone an excision biopsy of the primary tumour, FDG-PET showed no focal pathology. SWR-based images visualised 25 primary tumours in the remaining 27 patients, demonstrating a sensitivity of 92%. Both missed tumours were staged T1 on histopathological examination. On the OHR scans, 27 primary tumours were visualised, demonstrating a sensitivity of 100%. ***Figure 3a*** shows an example of improved visualisation of a primary tumour in the head and neck with OHR images.

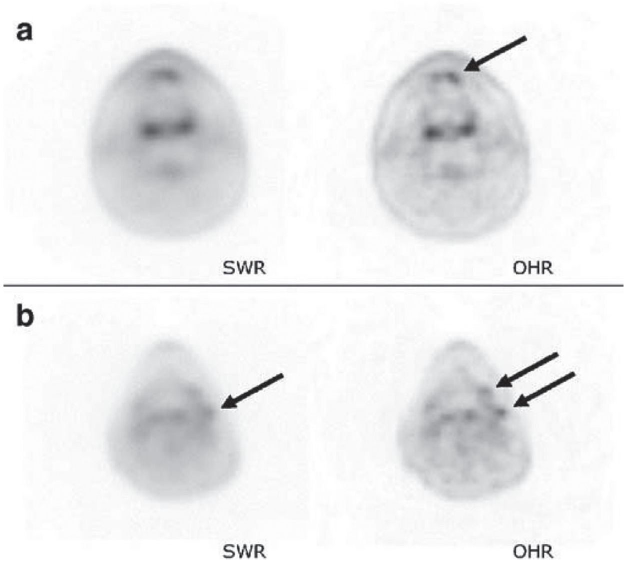

Figure 3: Example slices illustrating the improvement in image quality between reconstructions with SWR and OHR parameters in the head and neck area. **a** Patient with a T1 carcinoma of the left ventral tongue. On the SWR images the tumour was not distinguishable from physiological tongue muscle activity. By contrast, it was visible on the OHR images (arrow). **b** Patient with suspicion of one vague lymph node metastasis (arrow) on the SWR images. On the OHR images, multiple nodes were clearly visible (arrows). Note that physiological structures such as the tonsils are also more clearly visualised

	Primary tumour SUV_{max}			Primary tumour SUV_{mean}		
	SWR	**OHR**	**Increase**	**SWR**	**OHR**	**Increase**
1	7.6	10.0	32%	5.9	7.9	34%
2	3.9	6.2	59%	2.8	3.8	36%
3	2.8	4.4	57%	2.5	3.6	44%
4	11.0	21.3	94%	6.3	11.1	76%
5	1.0	1.2	20%	0.9	1.1	22%
6	1.9	2.6	37%	1.8	2.3	28%
7	2.9	4.5	55%	2.5	3.4	36%
8	3.2	3.1	-3%	3.1	2.8	-10%
9	2.7	4.1	52%	2.5	3.5	40%
10	6.4	10.0	56%	4.0	7.1	78%
11	11.7	16.1	38%	8.2	10.3	26%
12	**No SUV measurable**					
13	3.2	4.9	53%	2.6	3.8	46%
14	6.1	7.7	26%	4.2	5.0	19%
15	3.0	3.8	27%	2.3	2.9	26%
16	4.4	6.1	39%	3.2	4.2	31%
17	1.7	2.7	59%	1.6	2.4	50%
18	4.9	7.7	57%	3.4	4.6	35%
19	2.8	4.8	71%	2.3	3.1	35%
20	**No SUV measurable**					
21	2.6	4.1	58%	2.1	3.1	48%
22	3.6	4.2	17%	3.0	3.5	17%
23	9.9	12.1	22%	7.8	9.7	24%
24	**No SUV measurable**					
25	8.3	9.5	14%	4.9	6.4	31%
26	10.9	11.7	7%	7.0	8.6	23%
27	5.8	9.0	55%	4.1	5.4	32%
28	8.5	12.4	46%	6.4	7.6	19%
Avg	5.2	7.4	42%	3.8	5.1	34%

Table 3: SUVs measured in visualised primary tumours, in SWR images and in OHR images

As shown in ***table 3***, on the SWR images the mean of the SUV_{mean} of all detected primary tumours was 3.8 (range 0.9–8.2) and the mean of the SUV_{max} was 5.2 (range 1.0–11.7). On the OHR images, the mean of the SUV_{mean} was 5.1 (range 1.1–11.1) and the mean of the SUV_{max} was 7.4 (range 1.2–21.3). Using OHR, the SUV_{mean} increased by 34% ($P<0.0001$) and the SUV_{max} increased by 42% ($P<0.0001$). As shown in ***figure 4***, there was a strong linear correlation between the SUV_{mean} values derived from SWR and OHR images ($r=0.96$), and between the SUV_{max} values derived from SWR and OHR images ($r=0.94$).

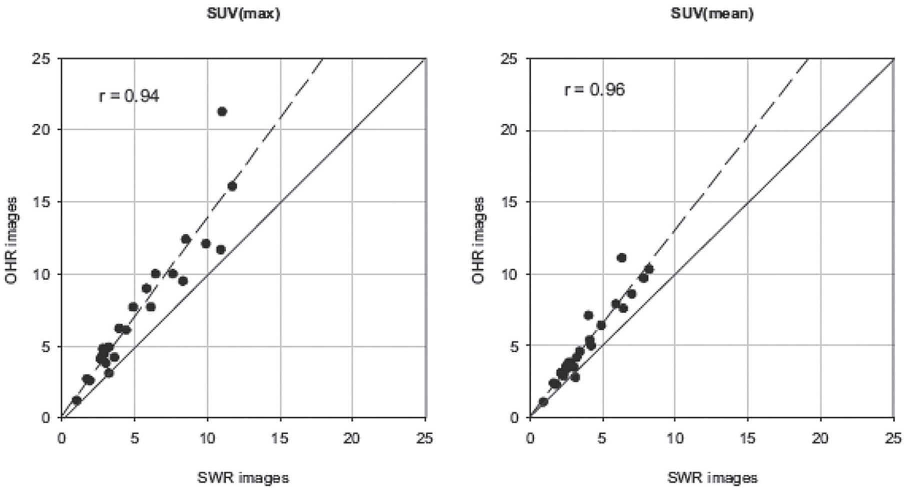

Figure 4: The relation between measured SUVs of detected primary tumours in the head and neck area, on SWR and OHR images. There is a strong correlation between the values on SWR and OHR images, though the OHR values are markedly higher than the SWR values. **Left**: SUV_{max}; **right**: SUV_{mean}

Lymph nodes

The SWR-based images visualised three lymph nodes in three patients, of which only one was confirmed as a lymph node metastasis on pathological examination. The OHR based images showed 14 lymph nodes in nine patients (in other words, 11 additional nodes in eight patients). Four of these patients were confirmed to have metastatic lymph nodes in the specified region. ***Figure 3b*** illustrates the improved visualisation of lymph node metastases in the head and neck on OHR images.

When calculated on a patient basis (e.g. accuracy for presence of lymph node metastases or not), sensitivity increased from 11% to 44% when using OHR images, while specificity decreased from 89% to 74%. The positive predictive value of the diagnostic procedure increased from 33% to 44% and the negative predictive value increased from 68% to 74%. The diagnostic performance of SWR and OHR images for the detection of lymph node metastases is summarised in ***table 4***.

	Patient basis		Involved neck side	
	SWR	OHR	SWR	OHR
Sensitivity (%)	11	44	9	45
Specificity (%)	89	74	96	87
Positive predictive value (%)	33	44	33	45
Negative predictive value (%)	68	74	81	87

Table 4: Diagnostic performance of FDG-PET in the detection of lymph node metastases on SWR images and OHR images. The values were calculated separately for detection of lymph nodes on a patient basis (e.g. presence of lymph node metastases or not) and on an involved neck side basis (e.g. having lymph node metastases on either the left or the right side)

With both reconstruction methods, specificity was relatively high, mainly because of a large number of true negatives. All missed lymph node metastases were very small, with a maximum diameter of 5 mm or less.

When calculated on the basis of the involved neck side (e.g. presence of lymph node metastases on either the left or the right side), sensitivity increased from 9% to 45% when using OHR images, while specificity decreased from 96% to 87%. The positive predictive value of the diagnostic procedure increased from 33% to 45% and the negative predictive value increased from 81% to 87%.

Overall, when considering primary tumours and lymph node metastases on a patient basis, the FDG-PET diagnosis was improved by using the OHR protocol in six patients (21%). The FDG-PET diagnosis worsened in three patients (11%), in all cases owing to visualisation of lymph nodes without metastasis.

Discussion

This study shows that a general reconstruction algorithm for whole-body studies may be less suitable for staging malignancies in the head and neck region. Using the SWR protocol, the sensitivity for the presence of lymph node metastases was only 11%, which is considerably lower than the findings reported by some other groups[2-5]. The presented results are therefore probably specific for our situation, reflecting, for example, the type of PET scanner and the standard reconstruction parameters used. Factors such as the aforementioned may also partially explain the variable results found in literature.

Using the OHR protocol we observed an increase in sensitivity for the detection of primary tumours, as well as an increase in sensitivity and specificity for the detection of lymph node metastases. From a clinical point of view, the most important improvements when using OHR were the increases in positive predictive value and negative predictive value for the presence of lymph node metastases. Where FDG-PET is used for staging, this will limit the number of missed N+ stages. The benefit is even more clearly expressed by the enhanced performance for the detection of the involved neck side, as this has a direct impact on patient management. Although not investigated in the current studies, similar effects may apply for relapse detection, re-staging and therapy monitoring. Perhaps equally as important as the better objective parameters is the possible subjective gain in reviewer confidence in image reading.

These beneficial effects may partially be explained by the higher spatial resolution of OHR-reconstructed FDG-PET images. Current clinical PET scanners have a spatial resolution of 4–7 mm full-width at half-maximum. The detection limit for small lesions is in the range of 4–10 mm, depending on scanner characteristics, localisation of the lesion and degree of FDG uptake by the lesion[11-13]. Although we have not evaluated objective changes in scanner spatial resolution, all lymph node metastases that were additionally detected with OHR had a diameter of 7 mm or smaller. Another important explanation for the benefits is the higher contrast resolution, as a better tumour to background ratio facilitates visual detection of lesions. This effect was quantitatively demonstrated by a statistically significant increase in SUV.

Although the OHR protocol delivers higher sensitivity for the detection of lymph node metastases, it results in a lower specificity due to visualisation of a larger number of small reactive lymph nodes. FDG accumulates in inflammatory cells such as activated granulocytes and macrophages[14], and this inherent characteristic of FDG will be difficult if not impossible to circumvent. Although false positive in oncological staging, from a pathophysiological point of view these lymph nodes are true positive. One can argue that intentional use of suboptimal image quality is not the preferred method to discriminate between reactive lymph nodes and metastases.

Several algorithms can be used for image reconstruction, such as filtered back-projection (FBP) or iterative ordered subset expectation maximisation (OSEM). The choice of image reconstruction algorithm and parameters influences the contrast resolution, spatial resolution and noise level. Nowadays, most investigators acknowledge that iterative reconstruction such as iterative OSEM yields the best image quality[15-18], although some discussion continues[19]. We limited this study to optimisation of iterative reconstruction, since FBP reconstruction has been abandoned.

In iterative reconstruction, three parameters are relevant: the number of iterations, the number of iteration subsets and the strength of the filter[20]. Essentially, increasing the number of iterations (and/or iteration subsets) improves spatial resolution and contrast resolution at the expense of higher noise levels and increased calculation time. Increasing the filter strength reduces noise at the expense of spatial resolution and contrast resolution. Reconstruction parameters are not generally applicable to all PET systems, as the results depend on camera characteristics, scanning mode, injected dose, the purpose of the scan and the personal preferences of the reviewer. Thus, optimisation of the diagnostic yield of FDG-PET by assessing on-site improvement of reconstruction parameters should be pursued.

Noise in PET images is mainly caused by photon attenuation and scatter, which strongly depend on the amount of attenuation (i.e. the patient's weight). The standard reconstruction parameters are chosen to render an optimal balance between noise levels, spatial resolution and contrast resolution, for an average patient. In the current study, more noise was observed in the OHR images by the reviewers. The somewhat higher increase in SUV_{max} as compared to SUV_{mean} also reflected increased statistical noise. This did not hinder adequate reporting, as was demonstrated by the improved diagnostic values. An increase in lesion SUV seems to improve the sensitivity for small lesions, especially in the range of the detection limit. This applies not only to FDG scanning: lesions with a poor SUV are likely to be present when using radiopharmaceuticals with a relatively low target-to-background ratio, such as 18F-3'-fluoro-3'-deoxy-thymidine (FLT)[21] or 18F-misonidazole. In these cases the improved algorithm may also be of value. The head and neck region is not the only area where improvement may be achieved. Adaptation of reconstruction parameters may also improve image quality in other situations with relatively low attenuation, e.g. in thin body parts (such as arms, legs and feet) or in patients with low body weight (cachectic patients, young children). An important difference, however, is the variable attenuation within these patients, as compared with the relatively uniform and stable size of the adult head and neck. This implies that a standard reconstruction protocol would be less desirable, but different parameters need to be investigated to optimise image quality.

Conclusions

Routine whole-body PET reconstruction parameters may prove inadequate for the head and neck area. By using image reconstruction parameters adapted to lower photon attenuation, major improvements may be achieved in image quality and diagnostic yield for the detection of small lesions. These improvements were shown to have an impact on staging and patient management. Additional separate reconstruction of the head and neck area with optimised parameters for specific clinical questions is advisable. This may also apply to image reconstruction of other small body parts or to whole-body studies in children.

Reference list

1. Stuckensen T, Kovacs AF, Adams S, Baum RP. Staging of the neck in patients with oral cavity squamous cell carcinomas: a prospective comparison of PET, ultrasound, CT and MRI. J Craniomaxillofac Surg 2000;28:319–24
2. Bruschini P, Giorgetti A, Bruschini L, Nacci A, Volterrani D, Cosottini M, et al. Positron emission tomography (PET) in the staging of head neck cancer: comparison between PET and CT. Acta Otorhinolaryngol Ital 2003;23:446–53
3. Teknos TN, Rosenthal EL, Lee D, Taylor R, Marn CS. Positron emission tomography in the evaluation of stage III and IV head and neck cancer. Head Neck 2001;23:1056–60
4. Braams JW, Pruim J, Freling NJ, Nikkels PG, Roodenburg JL, Boering G, et al. Detection of lymph node metastases of squamous-cell cancer of the head and neck with FDG-PET and MRI. J Nucl Med 1995;36:211–6
5. Laubenbacher C, Saumweber D, Wagner-Manslau C, Kau RJ, Herz M, Avril N, et al. Comparison of fluorine-18-fluorodeoxyglucose PET, MRI and endoscopy for staging head and neck squamous-cell carcinomas. J Nucl Med 1995;36:1747–57 1281
6. Stoeckli SJ, Steinert H, Pfaltz M, Schmid S. Is there a role for positron emission tomography with 18F-fluorodeoxyglucose in the initial staging of nodal negative oral and oropharyngeal squamous cell carcinoma. Head Neck 2002;24:345–9
7. Levin CS, Hoffman EJ. Calculation of positron range and its effect on the fundamental limit of positron emission tomography system spatial resolution. Phys Med Biol 1999;44:781–99
8. Sanchez-Crespo A, Andreo P, Larsson SA. Positron flight in human tissues and its influence on PET image spatial resolution. Eur J Nucl Med Mol Imaging 2004;31:44–51
9. Schoder H, Erdi YE, Chao K, Gonen M, Larson SM, Yeung HW. Clinical implications of different image reconstruction parameters for interpretation of whole-body PET studies in cancer patients. J Nucl Med 2004;45:559–66
10. Hudson HM, Larkin RS. Accelerated image reconstruction using ordered subsets of projection data. IEEE Trans Med Imag 1994;13:601–9
11. DeGrado TR, Turkington TG, Williams JJ, Stearns CW, Hoffman JM, Coleman RE. Performance characteristics of a whole-body PET scanner. J Nucl Med 1994;35:1398–406
12. Wienhard K, Dahlbom M, Eriksson L, Michel C, Bruckbauer T, Pietrzyk U, et al. The ECAT EXACT HR: performance of a new high resolution positron scanner. J Comput Assist Tomogr 1994;18:110–8
13. Boellaard R, Buijs F, de Jong HW, Lenox M, Gremillion T, Lammertsma AA. Characterization of a single LSO crystal layer high resolution research tomograph. Phys Med Biol 2003; 48:429–48
14. Kubota R, Yamada S, Kubota K, Ishiwata K, Tamahashi N, Ido T. Intratumoral distribution of fluorine-18-fluorodeoxyglucose in vivo: high accumulation in macrophages and granulation tissues studied by microautoradiography. J Nucl Med 1992;33: 1972–80
15. Hsu CH. A study of lesion contrast recovery for iterative PET image reconstructions versus filtered backprojection using an anthropomorphic thoracic phantom. Comput Med Imaging Graph 2002;26:119–27

16. Lartizien C, Kinahan PE, Swensson R, Comtat C, Lin M, Villemagne V, et al. Evaluating image reconstruction methods for tumor detection in 3-dimensional whole-body PET oncology imaging. J Nucl Med 2003;44:276–90
17. Riddell C, Carson RE, Carrasquillo JA, Libutti SK, Danforth DN, Whatley M, et al. Noise reduction in oncology FDG PET images by iterative reconstruction: a quantitative assessment. J Nucl Med 2001;42:1316–23
18. Etchebehere EC, Macapinlac HA, Gonen M, Humm K, Yeung HW, Akhurst T, et al. Qualitative and quantitative comparison between images obtained with filtered back projection and iterative reconstruction in prostate cancer lesions of 18F-FDG PET. Q J Nucl Med 2002;46:122–30
19. Schauwecker DS, Siddiqui AR, Wagner JD, Davidson D, Jung SH, Carlson KA, et al. Melanoma patients evaluated by four different positron emission tomography reconstruction techniques. Nucl Med Commun 2003;24:281–9
20. Boellaard R, Krak NC, Hoekstra OS, Lammertsma AA. Effects of noise, image resolution, and ROI definition on the accuracy of standard uptake values: a simulation study. J Nucl Med 2004;45:1519–27
21. Buck AK, Halter G, Schirrmeister H, Kotzerke J, Wurziger I, Glatting G, et al. Imaging proliferation in lung tumors with PET: 18F-FLT versus 18F-FDG. J Nucl Med 2003;44:1426–31 1282

CHAPTER 4.0

Diagnostic value of MR Lymphangiography in preoperative staging of clinically negative necks in squamous cell carcinoma of the oral cavity: a pilot study

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Abstract

Objective

Pilot study evaluating the diagnostic value of magnetic resonance lymphography (MRL) compared with conventional imaging techniques in the preoperative staging of the clinically (palpable) negative neck (cN0) in squamous cell carcinoma of the oral cavity (SCCOC).

Methods

Patients with SCCOC without clinical evidence of lymph node metastasis and scheduled for surgery underwent MRL in combination with ultrasound with or without fine needle aspiration cytology and multi-detector computer tomography. MRL images were interpreted by 2 independent radiologists. All patients were planned for resection of the primary tumor and a selective neck dissection of levels I–III. Histopathologic results were evaluated as the gold standard and compared with preoperative findings.

Results

One of nine evaluated patients had a metastatic node on histopathologic analysis. In all but 1 patient, MRL showed possible metastatic spread in at least 1 node. On a node-to-node basis, negative predictive value (NPV) and sensitivity reached 100% for 1.5- en 3-Tesla (T) MRL, specificity reached 92% at 1.5T and 93% at 3-T MRL, and positive predictive value (PPV) was 8% at 1.5-T MRL, for both radiologists. PPV at 3-T MRL was 10% and 9%, for radiologists I and II, respectively.

Conclusions

This prospective pilot study shows that MRL has a high NPV based on a node-to-node analysis. However, its PPV was only 10%, and therefore its use as a single imaging technique in the preoperative staging of the cN0 neck in SCCOC seems to be limited. Further studies are needed to confirm these data.

Introduction

Squamous cell carcinoma of the oral cavity (SCCOC) is responsible for almost 1% of new cancer cases in the Netherlands. The incidence of SCCOC is 4.1 per 100,000 in men and 2.7 per 100,000 in women[1]. The most important prognostic factor in SCCOC is probably the presence of cervical metastasis[2-4]. The choice of management depends largely on the presence and extent of metastatic disease in the neck. Identifying how extensive treatment should be for individual patients is of utmost importance. Therefore, treatment refinements, such as limitation of the field of radiation or a more selective neck dissection (SND) are necessary[5-8].
Palpably and radiologically negative necks (i.e. staged by ultrasound [US], with or without [+/−] fine needle aspiration cytology [FNAC]), and/or multi-detector computer tomography (MDCT), and/or magnetic resonance imaging [MRI]) show occult metastatic spread in 20–40%, which is discovered at postoperative histopathologic examination after neck dissection[9-19]. Modern imaging techniques have so far shown inadequate predictability in identifying cervical metastases in the absence of palpable lymph node [LN] metastases)[9-19]. A recent meta-analysis by de Bondt et al. showed that US (+/- FNAC) has the best accuracy for the detection of cervical lymph node metastases[20].
Promising results in detecting small metastases by using new MRI contrast agents (i.e. ultra-small superparamagnetic oxide nanoparticles [USPIO]) have recently been published[21, 22].
To date, the results in head and neck squamous cell carcinoma are sparse, but promising, with a reported sensitivity ranging from 86% to 96% and specificity from 77% to 100%[23-25]. However, these studies refer to heterogenic populations of patients with various head and neck malignancies that were mostly classified (using the Tumor Node Metastasis classification, TNM[26]) with >T2 primary tumors with clinically positive (cN+) necks, who were already being scheduled for therapeutic neck dissections. To our knowledge there are no previous studies reporting on the value of MRL in detecting occult metastatic disease in clinically N0 (cN0) SCCOC patients.
In the present prospective pilot study, we evaluate the added diagnostic value of MRL over conventional imaging methods, such as MDCT, MRI, and US (+/- FNAC) to detect occult metastatic disease in patients with cN0 necks in SCCOC.

Patients and methods

All patients diagnosed with a cN0 SCCOC between June 2005 and January 2007 and scheduled for SND I–III as part of their treatment were asked to participate in the study; informed consent was obtained from all patients and the study was approved by the local medical ethics committee.

Inclusion and exclusion criteria

The inclusion criteria were: (a) patients aged 18 years or older of either sex. Female patients were on effective contraception with a signed written informed consent; (b) patients with newly diagnosed, untreated SCCOC, which was histopathologically confirmed. All patients were scheduled to undergo excision of the primary tumor with SND I–III on the ipsilateral side within 21 days of MR imaging with the MRL contrast agent. No patient had clinical evidence of LN metastasis (routinely staged by means of palpation and US [+/- FNAC]) at the time of initial diagnosis (cN0).

The exclusion criteria were: (a) patients with a contraindication to MR imaging; (b) patients with a known allergy to dextran or drugs containing iron salts; (c) with hemochromatosis; (d) patients who underwent chemotherapy or radiotherapy before surgery; (e) patients who had a previous lymphadenectomy in the head and neck region; (f) female patients who were breast-feeding; (g) patients participating in another clinical trial, including that of another contrast preparation within the last 3 months or 7 days after this study; or (h) patients whose degree of cooperation was incompatible with the study.

All patients were preoperatively classified using the TNM classification[26]. Standard preoperative staging of the neck consisted of palpation and US (+/- FNAC). Conventional chest X-ray was performed to exclude pulmonary metastases. Imaging results of these modalities only were used to define treatment.

MDCT

On day 1, an MDCT scan (Siemens, Erlangen Germany) was performed from the anterior skull base to the aortic arch in 2-mm reconstructions in a soft tissue algorithm using 100 ml Optiray 300 (Mallinckrodt Medical, Dublin, Ireland; 2 ml/sec, delay 40 seconds). Nodes were described with reference to cervical LN level[27] and in relation to anatomical landmarks.

USPIO

After MDCT scanning, the USPIO (Ferumoxtran-10, SINEREM©, Guerbet, France) was administered to the patient. USPIO was provided as a lyophilized powder consisting of USPIO particles covered with low-molecular-weight dextran. The contrast agent (2.6 mg of iron/kg of body weight) was diluted in 100 ml of saline and intravenously administered in a single dose by drip infusion through a filter with a 4 ml/hour drip rate. USPIO was administered over 30 minutes in the presence of a physician.

MRI scanning

On day 2, 24–36 hours after USPIO administration, MRL was performed. Examinations were carried out at a field strength of 1.5 and 3.0 Tesla (T) in all patients using a head and neck surface coil (Avanto and Trio, Siemens, Erlangen, Germany, respectively). For MRL T2*-weighted gradient echo (GRE) multiple-echo data image combination MEDIC images were performed 24 hours after the administration of USPIO. As a precontrast MRL image, 2-dimensional (not influenced by T2* shortening and susceptibility artifacts) turbo spin echo (TSE) T1-true proton density (PD)-weighted images were used. The T1- and T2*- weighted MR images were each acquired in 2 planes, using identical position and resolution parameters, to enable comparison. Image planes were a semi-sagittal “sternocleidal” plane and an axial plane. For the USPIO-sensitive MRL images, a T2* (iron-sensitive) MEDIC was used. Additionally, a 3D (isometric voxel) T1-weighted GRE sequence (volumetric interpolated breath-hold examination) was applied. The scanned area extended from the clivus to the aortic arch. All sequences were performed after administration of the MRL contrast agent. See ***table 1*** for scanning parameters.

Sequence	Direction	B0 field (T)	TR (ms)	TE (ms)	Slice (mm)
T1-PD-pre	sag	1.5	411	9	3
T1-PD-pre	ax	1.5	453	14	4.4
T1-PD-pre	sag	3	704	13	2.5
T1-PD-pre	ax	3	1040	13	4.5
MEDIC T2*	sag	1.5	418	18	3
MEDIC T2*	ax	1.5	567	18	4.4
MEDIC T2*	sag	3	643	9.1	2.5
MEDIC T2*	ax	3	1210	9.1	4.5
VIBE T1 GRE	3D iso-ax	1.5	8.75	4.24	0.8 iso
VIBE T1 GRE	3D iso-ax	3	5.09	2.45	0.65 iso
fl-3D-MRA	3D iso cor	3	3.38	1.17	1.0 iso

Table 1: Scanning parameters of used sequences.

US and FNAC

US was performed immediately after MRL by using a linear 7.5-MHz probe (ATL HDI 5000, ATL Philips Healthcare, Eindhoven, the Netherlands). This procedure was performed as the final examination to prevent artifacts caused by the cytologic aspiration trauma and blood products. Cervical levels I–VI[27] were examined on both sides (with radiologists blinded to the MRL and MDCT results). All nodes were described by level and orientation in 2 directions (the long and short axes) in relation to the anatomical landmarks. If the short axis of a LN exceeded 5 mm in levels I, III–VI and 7 mm in level II, FNAC was performed. FNAC was limited to 1 LN on either side with a maximum of 2 nodes. If more LNs were enlarged, the node with the largest axial diameter was chosen for FNAC.

Image evaluation

All MRL, MDCT, and US examinations were evaluated by 2 radiologists (WD and RdB), experienced in head and neck radiology. They were blinded to each other's results and clinical information, such as stage, type, and localization of the primary tumor. All images were evaluated and scored on a node-to-node basis as described by Lahaye et al.[28] All LNs were described by level, orientation, and anatomical landmarks. The following criteria were used for suspicion of LN metastasis. For MDCT and MRI, nodes with a minimal axial diameter exceeding 10 mm for levels I, III–VI and 11 mm for level II, respectively, or detection of central necrosis, were considered to be malignant[13, 16, 19, 29]. For MRL, TSE-PD-T1-weighted (iron insensitive) and T2*-GRE (iron sensitive) images were compared. LNs were scored at 3 levels (A, B or C) in order to assess the level of suspicion (see ***figure 1*** [Lahaye et al.[28] and de Bondt et al.[30]]). LNs with a homogeneous signal intensity (SI) decrease on GRE images compared with SI on TSE images, with or without only small inhomogeneities (less than 30% of the node on its largest image) were considered normal[28, 31]. LNs with an area of 30% or more with no signal drop (i.e. category B and C) on GRE images were considered metastatic: nodes with an area of 30–50% of signal drop were scored 'B' and nodes with an area of >50% of signal drop were scored 'C'. A T1 flash 3D magnetic resonance angiography (MRA) sequence was used to display the anatomical location of the nodes in relation to the vessels to the surgeon preoperatively.

Figure 1: Different categories of nodal MRL staging (modified scheme from de Bondt et al.[30] and Lahaye et al.[28])

Surgical protocol

SND (as described by Medina and Byers[32]) of levels I–III was performed on the side affected by the primary tumor. If suspicious nodes were found at MRL outside the standard surgical field of view (i.e. homolateral levels I–III), but close to the midline, the SND was extended to incorporate the suspicious node. After the resection, the neck dissection specimen was pinned to a standardized grid of the neck and a digital photograph was taken of the specimen on the grid for correlation.

Histology

The pathologist manually identified and localized the LNs per neck level and anatomical landmark in the specimen in combination with the digital photograph in order to optimize node-to-node correlation. The maximum short axial diameter of all LNs in the dissection specimen was recorded, followed by fixation of LNs, sectioning, and hematoxylin–eosin (HE) staining. Hereafter, each LN was examined microscopically (4-µm specimens, every 2–3 mm) and the image digitalized. Special attention was paid to nodal characteristics: the presence of histiocytosis, follicular hyperplasia, and the amount of iron were scored, the latter by Perls' staining method. This histopathologic analysis was used as the gold standard to determine the LN status. The classification of the American Joint Committee on Cancer[26] was used for pN staging of the neck.

Combined data analysis

The results of the measurements on MRI, MDCT, and US (+/- FNAC) were subsequently compared with the results of MRL and the pathologic examination of the neck dissection specimens. Correlation was based on node-to-node analysis of neck levels. Combining the maximum short axial diameter and the exact location of each LN per neck level (in relation to the surrounding anatomic structures, such as blood vessels, muscles, and salivary glands) a topographic correlation for each LN between the histopathologic examination and the MRL, MDCT, US, and MRL images was made possible. Statistical analysis was performed using SPSS 16.0©.

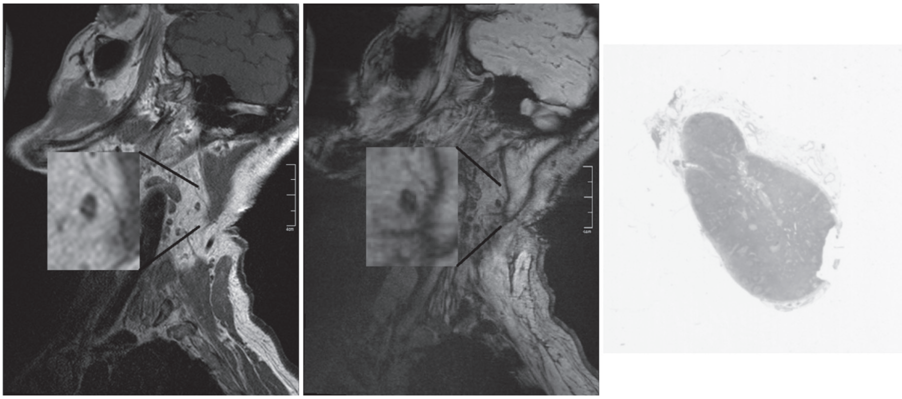
Results

Sixty-nine eligible patients were encountered. However, due to concurrent studies and a lack of interest and enthusiasm only eleven patients underwent MRL and conventional imaging; 2/11 were not surgically treated due to rapid growth of their primary tumor. Thus 9/11 patients were included (4 males, 5 females). Four tumors were clinically staged T2N0M0, 5 were staged T1N0M0. No tumor crossed the midline. Five tumors were located on the lateral side of the oral tongue, 2 in the floor of the mouth, 1 on the alveolar process and 1 in the buccal gingiva. One LN was found to contain metastatic cells during histopathologic analysis. Based on US, the radiologist found no reason to perform FNAC in 4/9 cases (44%). In the remaining 5, FNAC was performed revealing no metastatic cells. MDCT scanning showed 4 patients with possible metastatic nodes; in 3/4 cases FNAC was later performed during US investigation (and was negative); in 1 case, US did not indicate the positive node on CT as suspect and no FNAC was performed. US (+/- FNAC) correctly staged 8 necks as true-negative, 1 was false-negative; MDCT correctly staged 5 necks as true-negative, 3 were false-positive and 1 was true-positive. For an overview of preoperative imaging results, see ***table 2***.

Patient no.	T-stage	US	FNAC	CT	MRL 1.5T	MRL 3 T	Histopathological examination
I	1	-	NP	-	+	+	-
II	2	*	Neg	+	+	+	-
III	2	-	NP	-	+	+	-
IV	1	-	NP	-	+	+	-
V	2	*	Neg	-	+	+	-
VI	1	-	NP	+	+	+	-
VII	1	*	Neg	+	+	+	-
VIII	1	-	NP	-	-	-	-
IX	2	*	Neg	+	+	+	+

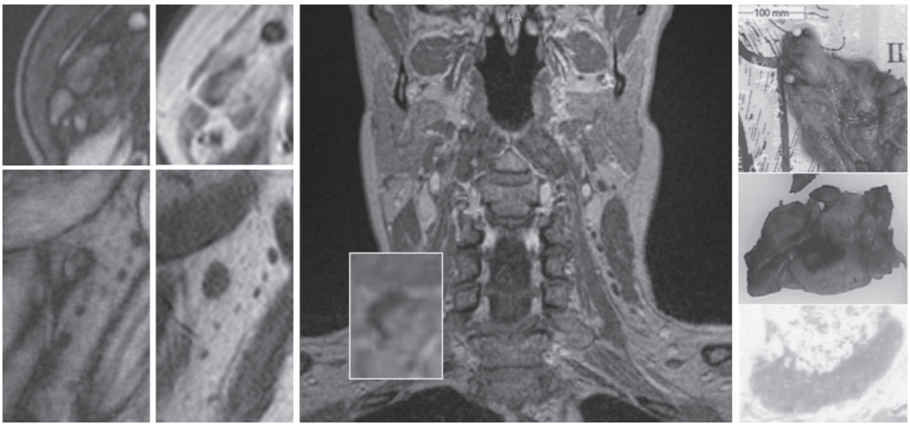
Table 2: Nine patients with their positive (+) or negative (-) preoperative staging modalities. Neg = no tumor cells. NP = Not Performed. US is scored '*' when size was reason to perform FNAC

No adverse events were recorded during the administration and use of USPIO.
With MRL, 1 patient was true-positive, 1 true-negative, and 7/9 were false-positive. On a node-to-node level, a total of 143 nodes were histopathologically correlated, of which 13/143 and 12/143 were scored positive by radiologist I and II, respectively, at 1.5-T MRL, and 10/143 and 11/143, respectively, at 3-T MRL. There were 3 patients with 1 node scored in the 'B' category: 1 at 3-T MR-imaging and 2 at 1.5-T MR-imaging: all 3 were scored negative on histopathalogical examination. The majority of suspicious nodes on MRL (either 1.5 or 3 T) had a minimal axial diameter of 4–6 mm.
There was only 1 histopathologically proven positive LN: this node was positively correlated and showed a minimal axial diameter of 8 mm at 1.5 T and 9 mm at 3 T and was scored as 'A' in both modalities. At postoperative histopathologic examination, the node was 12 mm in minimal axial diameter and showed extracapsular spread. Examples of MRL images are shown in ***figures 2 and 3***.



2A 2B 2C

Figure 2: Figure A shows a sagittal TSE-PD-weighted image of a normal level IIB 3 mm node with a high signal intensity (SI) center in the fatty hilum. In figure B, the high SI vanishes due to the fat saturation of the T2*-weighted sequence. Due to USPIO (iron) accumulation in the LN the entire node has a low SI on the T2*-weighted image corresponding with a non-metastatic node. Figure C is the corresponding hematoxylin–eosin macroscopic histology showing a normal lymph node. Due to the partial volume, the fat cells are not represented in the histological specimen.



3A 3B 3C 3D

Figure 3: Example of a false-positive lymph node on magnetic resonance lymphography.This figure demonstrates a lymph node in a patient (female 64 years, T1 tongue margin carcinoma) on level IIA, right. In figure A and B, this node (5 mm short axis) is shown in axial and sagittal view on (A) T2* and (B) T1-PDW TSE. This node has a bright hilum in the cortical area on T1 without signal drop on T2*. Figure D demonstrates the macroscopic resemblance of the lymph node. Histology showed a lymph node with small foci of chronic inflammation with foamy macrophages. These areas do not accumulate USPIO.

On a node-to-node analysis, no significant correlation could be found between any of the examined nodal characteristics (presence of histiocytosis, follicular hyperplasia, or the amount of iron) and false-positive results. All but 1 patient had at least 1 USPIO-positive suspicious node, both on 1.5- and 3-T MRL, with a maximum of 4 suspicious nodes in 1 patient. No false-negatives were found in this small group of patients leading to a negative predictive value (NPV) of 100% in both radiologists' results (for both 1.5- and 3-T imaging, node-to-node analysis). Node-to-node positive predictive value (PPV) reached 8% for both radiologists in 1.5-T interpretations. In 3-T imaging, PPV reached 10% and 9% for radiologist I and II, respectively. By node-to-node analysis a sensitivity of 100% (for both radiologists' results) is reached. Specificity was equal for both radiologists as well and reached 92% in 1.5-T imaging and 93% in 3-T imaging. For a comparison of both radiologists' results and the number of detected nodes, see ***table 3***.

Size node (mm smallest axial dm)	**A (1,5Tesla)**	**B (1,5Tesla)**	**C (1,5Tesla)**	**A (3Tesla)**	**B (3Tesla)**	**C (3Tesla)**
2	-/-	-/-	-/-	-/2	-/-	-/-
3	2/3	1/1	-/-	1/1	-/-	-/-
4	13/10	-/1	-/-	7/7	-/1	-/-
5	8/9	2/2	-/-	10/6	2/2	-/-
6	11/7	3/2	-/-	6/6	3/3	-/-
7	4/2	2/1	-/-	4/3	-/-	-/-
8	-/-	1/2	-/-	-/-	1/1	-/-
9	-/-	2/1	1/1	-/-	2/3	1/-
11	-/-	-/-	1/1	-/-	1/1	-/-
12	-/-	-/-	-/-	1/1	-/-	-/-
Total	38/31	11/10	2/2	29/26	9/11	1/0

Table 3: Results of MRL: number of nodes scored positive by reader I and **reader II**
A-C: categories of possible metastatic involvement in lymph nodes, see ***figure 1***

Discussion

We performed a pilot study on the use of MRL in cN0 SCCOC to investigate whether this preoperative imaging modality could have additional value to our standard workup consisting of palpation and US (+/- FNAC).

Many staging techniques have been under investigation and have been described for the preoperative staging of the cN0 neck in SCCOC in order to lower the amount of false-negative necks to 20% or less[33]: this could lead to a change in treatment for this group of patients by avoiding SND in patients with a cN0 neck, thereby reducing postoperative morbidity.

MRL has been shown to be a reliable tool to differentiate benign from malignant LNs in animals[34, 35] and in several human malignancies[21, 22, 36-38].

In the field of head and neck oncology, some studies have been performed with promising results: Mack et al.[23] analyzed a heterogenic group of 30 patients with a sensitivity of 86% and specificity of 100%.

A phase III, multicenter, clinical trial by Sigal et al.[24] showed a sensitivity of 88% and a specificity of 77% for MRL for imaging of individual LNs in 81 patients with different types of head and neck SCC with relatively high T-stages (11 T1, 29 T2, 28 T3, 10 T4, and 5 Tx tumors), of which 28 were cN0 (palpation only). Twelve patients had occult metastatic spread (42%). MRL in cN0 patients was less reliable when compared with the whole group. A study by Curvo-Semedo et al.[25] of 20 patients with different head and neck carcinomas (no SCCOC) showed a sensitivity of 96% and a specificity of 79%; accuracy was 86%. However, in their cohort, only 1 T1 tumor was included and 13 of 20 patients were staged cN+.

In our small though homogenic cohort, US (+/- FNAC) correctly identified 8/9 true-negative necks and MDCT correctly identified 4/9 true-negative necks. Considering our MRL results, the majority of 'suspect' LNs had a size well below the current malignancy criteria of MDCT, MRI, and US (+/- FNAC) for LNs of the neck with metastatic spread; in addition, the (considered) metastatic part of the lymph node in the majority of nodes was even smaller (30–50% of the already small node).

The 1 histopathologically confirmed metastatic node was positively identified by MRL: this fact seems of little importance considering the high amount of false-positive results.

There could be a number of reasons for the high amount of false-positives: the amount of LNs in the head and neck region is higher than in the pelvic area, and probably more susceptible to inflammatory changes due to, for instance, frequently occurring upper airway infections. Chronically active LNs (due to, for instance, chronic rhinosinusitis or chronic tonsillitis) could cause changes in the uptake of USPIO. It is thought that this is caused by a reduced uptake of USPIO due to hyperplasia of the germinal centers, and lack of macrophages in that center; macrophages only appear in the periphery of the node[24, 25]. A different USPIO uptake by macrophages in the LNs of the neck might also explain some of the differences: for instance hyaline metamorphosis (e.g. conversion of cells and intercellular substance into hyaline material, possibly due to recurrent infections or malnutrition) might cause false-positive results, as could focal fibrosis or focal granulomatosis[28]; however, we could not confirm this finding during our histopathologic research. Benign space-occupying lesions, such as sinus histiocytosis or extensive follicular hyperplasia, seemed to play no role in false-positive results in our study. In a study by Rety et al.[39], differences in distribution by USPIO were described. In their study, subdiaphragmatic LNs exhibited a higher uptake than supradiaphragm LNs. Furthermore, Wagner et al.[40] described that after an intravenous injection, nanoparticle uptake in central LNs (mesenteric and mediastinal) is always higher than in peripheral LNs. An important explanation may also be the possible lack of sensitivity of the current 'gold standard' of histopathologic examination: perhaps more small metastatic nodes would be identified by adding immunohistochemistry and multi-slice sectioning of all LNs.

The limitations of our study are the small sample size and the fact that only 1 node was a metastasis. Furthermore, only T1 and T2 tumors were included, which could bias the results for the whole cN0 group of patients. In patient groups with a higher pretest probability of metastatic disease (cN+ necks) USPIO-enhanced MRL has been proven to perform better[23-25]. The fact that no immunohistochemistry and multi-slice sectioning were performed and unfortunately, the lack of histopathologic explanation for the high number of false-positive findings also are limitations to the study. Finally, the used interpretation scheme for measurement of metastatic spread in LNs, which is different from that described by, for instance, Harisinghani et al.[41] and Heesakkers et al.[31] may have influenced the results. However, no study has focused on this specific cN0 SCCOC group of patients and performed a node-to-node analysis before.

A negative preoperative MRL might prove to be an indicator of a truly histopathologically proven negative neck and could perhaps, if future research would confirm our findings, lead to less SNDs being performed. The combination of MRL (with a high sensitivity) with US (+/- FNAC) (with a high specificity) might prove to be useful in preoperative assessment. However, a lot of preoperative scans would have to be performed to identify 1 truly negative neck. Research in a larger cohort is mandatory.

Production of the USPIO contrast agent by Guerbet (SINEREM©, France) was recently discontinued. However, new USPIO agents with comparable characteristics will become available in the near future.

Conclusions

This pilot study shows that MRL, in its current form, in low-stage SCCOC has a high amount of false-positive results when compared with standard imaging and histopathologic analysis. However, its NPV and sensitivity in this small group of patients seem high and a combination with US (+/- FNAC) might prove to be promising. More research confirming these results and concerning the rationale behind the high amount of false-positive findings is needed.

Reference List

1. Knegt PP, Keus RB, Roodenburg JL. [The practice guideline 'Carcinoma of the oral cavity and oropharynx']. Ned Tijdschr Geneeskd 2006 Jan 14;150(2):83-8.
2. Leemans CR, Tiwari R, Nauta JJ, et al. Regional lymph node involvement and its significance in the development of distant metastases in head and neck carcinoma. Cancer 1993 Jan 15;71(2):452-6.
3. Snow GB, Annyas AA, van Slooten EA, et al. Prognostic factors of neck node metastasis. Clin Otolaryngol 1982 Jun;7(3):185-92.
4. Leemans CR, Tiwari R, Nauta JJ, et al. Recurrence at the primary site in head and neck cancer and the significance of neck lymph node metastases as a prognostic factor. Cancer 1994 Jan 1;73(1):187-90.
5. Newman JP, Terris DJ, Pinto HA, et al. Surgical morbidity of neck dissection after chemoradiotherapy in advanced head and neck cancer. Ann Otol Rhinol Laryngol 1997 Feb;106(2):117-22.
6. Hillel A, Patten C. Neck dissection: morbidity and rehabilitation. Cancer Treat Res 1990;52:133-47.
7. Byers RM, Wolf PF, Ballantyne AJ. Rationale for elective modified neck dissection. Head Neck Surg 1988 Jan;10(3):160-7.
8. Ferlito A, Rinaldo A, Robbins KT, et al. Changing concepts in the surgical management of the cervical node metastasis. Oral Oncol 2003 Jul;39(5):429-35.
9. Merritt RM, Williams MF, James TH, et al. Detection of cervical metastasis. A meta-analysis comparing computed tomography with physical examination. Arch Otolaryngol Head Neck Surg 1997 Feb;123(2):149-52.
10. van den Brekel MW, Castelijns JA, Stel HV, et al. Occult metastatic neck disease: detection with US and US-guided fine-needle aspiration cytology. Radiology 1991 Aug;180(2):457-61.
11. Baatenburg de Jong RJ, Rongen RJ, Lameris JS, et al. Metastatic neck disease. Palpation vs ultrasound examination. Arch Otolaryngol Head Neck Surg 1989 Jun;115(6):689-90.
12. Baatenburg de Jong RJ, Rongen RJ, Verwoerd CD, et al. Ultrasound-guided fine-needle aspiration biopsy of neck nodes. Arch Otolaryngol Head Neck Surg 1991 Apr;117(4):402-4.
13. van den Brekel MW, Castelijns JA, Stel HV, et al. Modern imaging techniques and ultrasound-guided aspiration cytology for the assessment of neck node metastases: a prospective comparative study. Eur Arch Otorhinolaryngol 1993;250(1):11-7.
14. Kyzas PA, Evangelou E, axa-Kyza D, et al. 18F-fluorodeoxyglucose positron emission tomography to evaluate cervical node metastases in patients with head and neck squamous cell carcinoma: a meta-analysis. J Natl Cancer Inst 2008 May 21;100(10):712-20.
15. Righi PD, Kopecky KK, Caldemeyer KS, et al. Comparison of ultrasound-fine needle aspiration and computed tomography in patients undergoing elective neck dissection. Head Neck 1997 Oct;19(7):604-10.
16. Takes RP, Righi P, Meeuwis CA, et al. The value of ultrasound with ultrasound-guided fine-needle aspiration biopsy compared to computed tomography in the detection of regional metastases in the clinically negative neck. Int J Radiat Oncol Biol Phys 1998 Mar 15;40(5):1027-32.
17. Knappe M, Louw M, Gregor RT. Ultrasonography-guided fine-needle aspiration for the assessment of cervical metastases. Arch Otolaryngol Head Neck Surg 2000 Sep;126(9):1091-6.

18. Wensing BM, Vogel WV, Marres HA, et al. FDG-PET in the clinically negative neck in oral squamous cell carcinoma. Laryngoscope 2006 May;116(5):809-13.
19. van den Brekel MW. Lymph node metastases: CT and MRI. Eur J Radiol 2000 Mar;33(3):230-8.
20. de Bondt RB, Nelemans PJ, Hofman PA, et al. Detection of lymph node metastases in head and neck cancer: a meta-analysis comparing US, USgFNAC, CT and MR imaging. Eur J Radiol 2007 Nov;64(2):266-72.
21. Heesakkers RA, Futterer JJ, Hovels AM, et al. Prostate cancer evaluated with ferumoxtran-10-enhanced T2*-weighted MR Imaging at 1.5 and 3.0 T: early experience. Radiology 2006 May;239(2):481-7.
22. Barentsz JO, Futterer JJ, Takahashi S. Use of ultrasmall superparamagnetic iron oxide in lymph node MR imaging in prostate cancer patients. Eur J Radiol 2007 Sep;63(3):369-72.
23. Mack MG, Balzer JO, Straub R, et al. Superparamagnetic iron oxide-enhanced MR imaging of head and neck lymph nodes. Radiology 2002 Jan;222(1):239-44.
24. Sigal R, Vogl T, Casselman J, et al. Lymph node metastases from head and neck squamous cell carcinoma: MR imaging with ultrasmall superparamagnetic iron oxide particles (Sinerem MR) -- results of a phase-III multicenter clinical trial. Eur Radiol 2002 May;12(5):1104-13.
25. Curvo-Semedo L, Diniz M, Migueis J, et al. USPIO-enhanced magnetic resonance imaging for nodal staging in patients with head and neck cancer. J Magn Reson Imaging 2006 Jul;24(1):123-31.
26. Sobin LH WC. International Union Against Cancer (UICC): ''TNM classification of malignant tumors.'' 6th ed. 2002. Ref Type: Generic
27. Som PM, Curtin HD, Mancuso AA. Imaging-based nodal classification for evaluation of neck metastatic adenopathy. AJR Am J Roentgenol 2000 Mar;174(3):837-44.
28. Lahaye MJ, Engelen SM, Kessels AG, et al. USPIO-enhanced MR imaging for nodal staging in patients with primary rectal cancer: predictive criteria. Radiology 2008 Mar;246(3):804-11.
29. van den Brekel MW, Castelijns JA, Snow GB. The size of lymph nodes in the neck on sonograms as a radiologic criterion for metastasis: how reliable is it? AJNR Am J Neuroradiol 1998 Apr;19(4):695-700.
30. de Bondt RB, Nelemans PJ, Bakers F, et al. Morphological MRI criteria improve the detection of lymph node metastases in head and neck squamous cell carcinoma: multivariate logistic regression analysis of MRI features of cervical lymph nodes. Eur Radiol 2009 Mar;19(3):626-33.
31. Heesakkers RA, Hovels AM, Jager GJ, et al. MRI with a lymph-node-specific contrast agent as an alternative to CT scan and lymph-node dissection in patients with prostate cancer: a prospective multicohort study. Lancet Oncol 2008 Sep;9(9):850-6.
32. Medina JE, Byers RM. Supraomohyoid neck dissection: rationale, indications, and surgical technique. Head Neck 1989 Mar;11(2):111-22.
33. Weiss MH, Harrison LB, Isaacs RS. Use of decision analysis in planning a management strategy for the stage N0 neck. Arch Otolaryngol Head Neck Surg 1994 Jul;120(7):699-702.
34. Weissleder R, Elizondo G, Wittenberg J, et al. Ultrasmall superparamagnetic iron oxide: an intravenous contrast agent for assessing lymph nodes with MR imaging. Radiology 1990 May;175(2):494-8.
35. Vassallo P, Matei C, Heston WD, et al. AMI-227-enhanced MR lymphography: usefulness for differentiating reactive from tumor-bearing lymph nodes. Radiology 1994 Nov;193(2):501-6.

36. Kimura K, Tanigawa N, Matsuki M, et al. High-resolution MR lymphography using ultrasmall superparamagnetic iron oxide (USPIO) in the evaluation of axillary lymph nodes in patients with early stage breast cancer: preliminary results. Breast Cancer 2009 Jul 3.
37. Koh DM, Brown G, Temple L, et al. Rectal cancer: mesorectal lymph nodes at MR imaging with USPIO versus histopathologic findings--initial observations. Radiology 2004 Apr;231(1):91-9.
38. Deserno WM, Harisinghani MG, Taupitz M, et al. Urinary bladder cancer: preoperative nodal staging with ferumoxtran-10-enhanced MR imaging. Radiology 2004 Nov;233(2):449-56.
39. Rety F, Clement O, Siauve N, et al. MR lymphography using iron oxide nanoparticles in rats: pharmacokinetics in the lymphatic system after intravenous injection. J Magn Reson Imaging 2000 Nov;12(5):734-9.
40. S. Wagner, D. Pfefferer, W. Ebert et al. Intravenous MR lymphography with superparamagnetic iron oxide particles: experimental studies in rats and rabbits. European Radiology 1994 Jul;5(6):640-6
41. Harisinghani MG, Barentsz J, Hahn PF, et al. Noninvasive detection of clinically occult lymph-node metastases in prostate cancer. N Engl J Med 2003 Jun 19;348(25):2491-9.

CHAPTER 5.0

Oral squamous cell carcinoma and a clinically negative neck: the value of follow-up

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Abstract

Objective

In squamous cell carcinoma of the oral cavity (SCCOC) regular follow-up comprises 5 years of prescheduled visits regardless of tumor stage and/or treatment. We analyzed our standard treatment- and follow-up protocol in patients with a preoperative clinically negative neck (cN0) in SCOCC.

Methods

This is a retrospective chart analysis. Inventarisation of treatment, occult metastatic spread and follow-up was performed.

Results

One-hundred-and-ninety-seven patients were included. The occult metastatic rate was 24%. Eighty-three percent of recurrent disease presented within 2 years. Fifty-three percent of the patients with recurrent disease visited their physician outside prescheduled control visits.

Conclusions

Ultrasound-guided fine needle aspiration cytology currently is one of the most reliable staging techniques in cN0 SCCOC. Regular follow-up could perhaps be limited from 5 to 2 years of prescheduled follow-up visits.

Introduction

One of the most controversial items in head and neck remains the treatment of the clinically negative neck (cN0) in squamous cell carcinoma of the oral cavity (SCCOC) due to the presence of occult metastases. Control of the primary tumor can usually be achieved by surgery and in some cases by radiotherapy. Tumor treatment failure is often due to metastatic spread to cervical lymph nodes, reducing survival by approximately 50%[1-3]. Management of the cN0 neck is therefore considered crucial. Three options are available: elective neck dissection, primary radiotherapeutic treatment or a 'wait-and-see' policy. The rationale behind the latter is that 60-80% of patients who undergo elective neck dissection are in fact being overtreated, leading to increased morbidity. A 'wait-and-see' policy requires careful monitoring of the neck over time, in combination with ultrasound (US) and/or ultrasound-guided fine needle aspiration cytology (FNAC). Should a positive lymph node be detected during follow-up, different types of salvage neck dissection can be performed. With this strategy, some studies have found recurrence rates comparable to those for elective treatment of the neck[4,5].

However, other studies (which did not include US (+/- FNAC) during follow-up for the neck) reported lower survival rates in patients following a wait-and-see policy[6,7] when compared to patients treated by elective neck dissection.

Given these considerations, we have firstly evaluated the results of our standard surgical treatment with elective neck dissection for patients suffering from SCCOC. We furthermore especially focused on the recurrence rate of regional disease following elective neck dissection with special emphasis on the follow-up schedule which is advocated in the national guideline for oral carcinoma issued by the Dutch Cancer Society.

Materials and methods

In this retrospective study, the medical records of all consecutive patients with histologically proven SCC of the OC who presented at the Radboud University Nijmegen Medical Center between 1st January 1992 and 1st December 2004 were reviewed. Patients with a cN0 neck staged through palpation and US who underwent selective neck dissection of levels I-III (supraomohyoidal neck dissection [SOHND]) as described by Medina et al.[8], as a staging procedure and as part of their treatment, were included. In all cases a preoperative US (+/- FNAC) examination of the neck was performed. If a suspicious lymph node (or nodes) with a minimum diameter > 5 mm was found by US, fine needle aspiration cytology was performed. A conventional chest X-ray was performed in every patient. CT and/or MRI scanning were performed only in case of doubts concerning primary tumor extension (e.g. bone involvement). Patients who had suffered from head and neck squamous cell carcinoma (HNSCC) five years prior to their current treatment or who had received radiotherapeutic or chemotherapeutic treatment for any kind of disease during this period were excluded.

Surgery was performed by five experienced head and neck surgeons. In the majority of cases a frozen stage section (FSS) of the neck specimen was performed during the operation: suspicious nodes and/or the largest jugulodigastric and most distal jugulo-omohyoid node were sampled. If FSS during the operation revealed metastatic disease, selective neck dissection of levels I-III was routinely extended to a modified radical neck dissection (MRND), encompassing levels I-V. After the resection specimen had undergone standardized marking, it was sent to the department of pathology where it was examined using standardized sectioning and haematoxylin eosin (HE) staining.

The detection of two or more histopathologically confirmed metastatic lymph nodes and/or the presence of extracapsular spread (ECS) were absolute indications for post-operative radiotherapeutic treatment. Tumor-positive resection margins were an indication for radiotherapeutic treatment of the primary site. Relative indications for postoperative radiotherapeutic treatment were: tumor invasion of the mandible, one metastatic lymph node, close resection margins (<5 mm), angiolymphatic invasion, perineural invasion and a diffuse pattern of tumor growth. Local recurrence is defined as a recurrence at the original site within 5 years following therapeutic excision. After this time, local tumor growth is considered to be a secondary primary tumor. Regional recurrence is defined as metastatic neck disease which does not affect structures of the oral cavity. Distant metastasis is defined as tumor spread from the primary tumor to distant organs or distant lymph nodes (e.g. not the neck).

The recommended follow-up comprises 5 years of regular prescheduled visits[9]. The minimum follow-up period in this study was 5 years. Our standard follow-up schedule consisted of visits every 2 months during the first year after surgical treatment, every 3 months during the second year, every 4 months during the third year and every 6 months during the fourth and fifth year. Hereafter, in the absence of any signs of recurrence or metastatic spread, patients were discharged.

Survival curves were estimated with the Kaplan-Meier approach based on overall survival (OS) and disease-free survival (DFS). OS was calculated from the date that patients were surgically treated, while DFS was calculated using the date of detection of recurrent disease. Log rank tests were used to compare the study groups.

Results

One hundred and ninety-seven patients were included: 125 males (63%) and 72 females (37%). Their age ranged from 27 to 90 years at the time of their operation (mean age: 62 years). The distribution of T-stages and tumor locations is shown in ***table 1***.

c TN-stage	Retromolar trigone	Floor of the mouth	Lateral tongue	Alveolar process	Buccal mucosa	Total
TxN0M0	0	1	1	0	0	2
T1N0M0	8	18	33	2	1	62
T2N0M0	7	47	41	4	4	103
T3N0M0	0	6	10	1	0	17
T4N0M0	5	4	0	4	0	13
Total	20	78	85	11	5	197

Table 1: preoperative clinical TNM-classification and location of 197 primary tumors

All patients were preoperatively staged cN0 through palpation and US. In 50 out of 197 cases (25%; 220 necks) US (+/- FNAC) was performed. A total of 48 neck specimens (24% of patients) showed regional metastatic spread during postoperative histopathological examination; 1 specimen was bilaterally positive (49 pN+ necks).
In a total of 30 T3 and T4 tumors five times a Thiersch graft was used to close the site of the excised primary tumor. In 16 cases extensive reconstructive surgery of the primary site was performed: 10 free flap soft tissue transfers were performed, as were 6 bone reconstructions, combined with soft tissue reconstructions. In 9 of these 30 cases the wound could be closed primarily.
In total, 76 metastases were found in 48 patients. No metastatic nodes were found in additionally resected neck levels (levels IV and V), performed after positive FSS. Histopathological staging of the neck yielded the following findings: 149 pN0, 33 pN1, 14 pN2b and 1 pN2c (68 stage I, 63 stage II, 36 stage III and 30 stage IVA tumors).
Twenty-two patients had absolute indications for postoperative radiotherapeutic treatment based on their neck staging (7 had one metastasis with ECS, 4 had two or more metastatic lymph nodes with ECS, and 11 cases had more than 2 tumor-positive nodes). Fifteen of these 22 patients actually received postoperative radiotherapeutic treatment (one of the remaining 7 patients died shortly after surgery due to massive aspiration and the condition of the other 6 patients was too poor to administer adequate treatment). Sixty-two patients received radiotherapeutic treatment based on primary tumor characteristics.
Forty patients (20% of patients) suffered from local, regional or distant recurrence. For an overview of their respective cT- and pTN-stages, see ***table 2***.
Fourteen of these patients initially presented with regional recurrence (7% of 197 patients). Of 149 pN0 necks, 9 patients (6%) developed initial regional recurrent disease, while 3 of the 48 patients with pN+ necks (6%) initially presented with regional recurrence. In 1 of these 12 patients level IV (combined with level III) showed metastatic disease. Two more patients presented with regional recurrent disease, but

also suffered from a secondary primary tumor and the origin of regional disease was unclear. Six of 30 patients who had undergone extensive reconstructive surgery suffered from recurrence: 3 local recurrences and 3 regional recurrences.

No. of tumors cTNM	pT1N0	pT2N0	pT3N0	pT4N0	pT1N1
TxN0M0	0	0	0	1	0
T1N0M0	4	3	0	1	2
T2N0M0	2	10	0	0	1
T3N0M0	0	1	0	1	0
T4N0M0	0	1	0	1	0
Total	6	15	1	3	3

Table 2: Distribution of clinical and pathological TNM stages in 40 patients suffering from recurrent disease

Twenty-four patients initially presented with a local recurrence (12% of 197 patients), while the remaining 2 patients had distant metastatic disease only without locoregional residual disease.

Fourteen of the 40 patients with recurrent disease were palliatively treated (35%). Nineteen patients with recurrent disease underwent salvage surgery and 9 of these patients also received radiotherapeutic treatment. Six patients received curative radiotherapeutic treatment. One patient was treated in a different hospital for recurrent disease and was lost to follow-up.

Of the 19 patients treated by salvage surgery with or without additional radiotherapeutic treatment, 11 died of recurrent disease (58%), a further 2 died of a second primary tumor, 1 died of an unrelated disease. Five of these 19 patients were disease-free at the end of follow-up. All 6 patients treated with curative intent by radiotherapy died of recurrent disease. In total, 17 of 25 curatively-treated patients (68%) died because of recurrent disease, 5 were alive and free of disease at the end of follow-up, 2 died from second primary tumors and 1 patient died due to cardiovascular disease. This means that 20 out of 25 patients (80%) were dead within 5 years of treatment for recurrent disease. In other words, 78% of patients presenting with recurrent disease died a tumor-related death.

The mean follow-up duration was 46 months (3.8 years; median 60 months, minimum of 0 months, maximum of 60 months). The mean time between primary curative surgery and appearance of recurrent disease was 15 months (1.25 years; median 10 months, minimum 2 months, maximum 58 months). Eighty percent of recurrences appeared within 20 months after primary curative surgery, 83% within 2 years from treatment and 90% within 3 years from treatment.

pT2N1	**pT4N1**	**pT2N2b**	**pT3N2b**	**pT4N2b**	
0	0	0	0	0	
0	0	0	0	0	
4	0	5	0	0	
0	0	0	1	0	
0	1	0	0	1	
4	1	5	1	1	**40**

In terms of presentation of recurrent disease, 16 patients (40%) presented with signs of recurrent disease during prescheduled routine visits. Twenty-one patients (53%) visited their oncologist at their own request with symptoms related to their recurrent disease, and for 3 patients (7%) it was not possible to ascertain when the recurrent disease was detected in these patients.
Finally, figures 1 and 2 show the overall survival and disease-free survival, respectively, in cN0 SCC of the OC. Five-year overall survival was 67% (***figure 1***). Five-year disease-free survival was 93, 80, 85 and 63% in stage I-IVA respectively (***figure 2***).

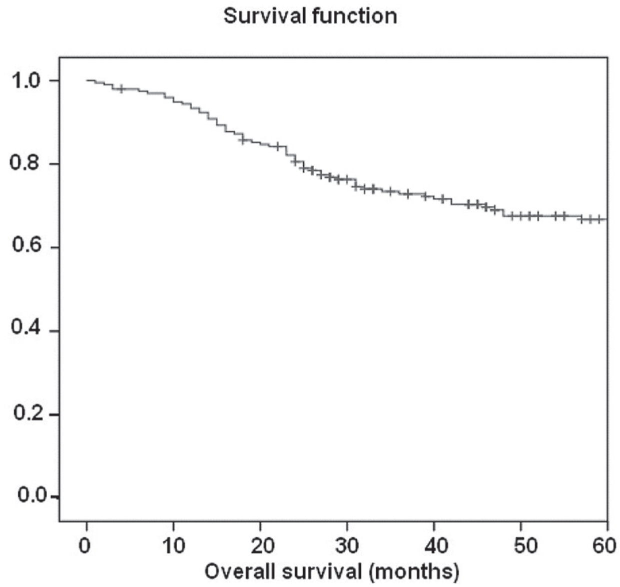

Figure 1: cumulative overall survival (months)

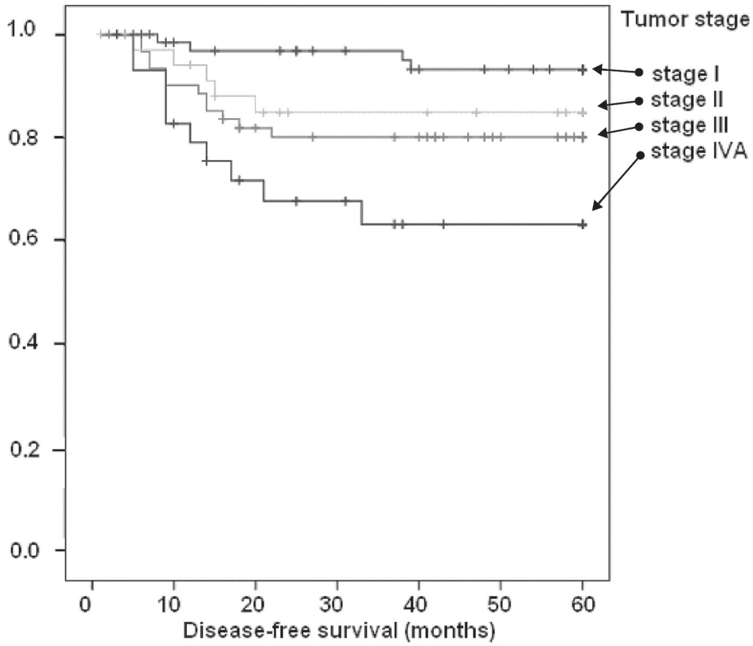

Figure 2: cumulative disease-free survival (months) related to post-operative tumor stage

Discussion

Our results confirm that, to date, selective neck dissection of levels I-III (formerly SOHND) remains the most important diagnostic tool in clinically N0 squamous cell carcinoma of the oral cavity. In a widely-accepted proposed treatment strategy, Weiss et al.[10] estimate that if there is a greater than 20% probability of finding occult metastatic spread during histopathological examination of cN0 necks in SCC of the OC, elective treatment of the neck should be performed. The preoperative use of US (+/- FNAC) combined with standard histopathological examination of the dissection specimen revealed a comparable percentage of occult metastases when compared to preoperative staging by CT, MRI or FDG-PET followed by histopathological staging[4,5,11-15], although its use is still not widely accepted. This finding has been previously mentioned by authors such as van den Brekel et al.[4,5] and Nieuwenhuis et al.[16] who even propose a 'wait-and-see' policy for a cN0 neck in certain cases of head and neck SCC.

In the current study the percentage of occult metastatic spread and recurrent disease is comparable to previously-published data[12,14,17].

Six percent of patients with a pN0 neck as well as 6% of patients with a pN+ neck developed an initial regional recurrence. If more sensitive histopathological techniques would have been used (like for instance the use of immunohistochemistry and improved serial sectioning) perhaps more pN+ necks would have been identified. Selective neck dissection would then have been even more therapeutic than we think since those necks, scored pN0, do not show more recurrent disease than pN+ necks of which most are additionaly treated.

We found no so-called 'skip metastases' in our neck dissection specimens: of course, aforementioned limitations of standard histopathological workup could also influence these numbers. Furthermore, only 1 initial regional recurrence involved level IV and therefore, in this group of patients, addition of level IV to standard treatment of the neck (as proposed by a number of authors[21,22]) does not seem justified. With postoperative radiotherapeutic treatment on indication this group of cN0 SCCOC has a 5-year disease-free survival of 83%.

The main goal of strict follow-up schedules would be to signal recurrent disease at an early stage, preferably leading to more successful salvage treatment. More than half of the patients who had recurrent disease made an extra appointment that led to the detection. Despite salvage treatment, however, survival rates decline dramatically with recurrent disease. This leads to questions regarding the follow-up schedule proposed in the Dutch national guideline for oral cavity carcinoma issued by the Dutch Cancer Society. For example, could prescheduled visits be limited? Could patients be better informed about the signs of possible recurrent disease and could regular visits even be abandoned?

In terms of costs, 76% of patients in this study with cN0 oral cavity carcinoma underwent elective treatment of the neck without any signs of postoperative metastatic spread.

Sixty-three percent of patients (124/197) remained disease-free postoperatively during follow-up. In other words, 63% of patients were intensively followed during the course of 5 years, involving high costs. Van den Brekel et al.[5] showed that in a group of mainly T1 and T2 oral tumors strict follow-up of the neck using US (+/- FNAC) every 2 to 5 visits (prescheduled visits every 4-8 weeks during the first year) could possibly replace elective neck dissection. In terms of our cohort, this would imply a total of 992 visits (8 visits per year on average), 310 ultrasounds (2.5 per year on average) and at least as many fine needle aspiration biopsies in 124 disease-free patients during the first year of follow-up alone. Of course, in case of more advanced c- and pTN stages, especially after extensive reconstructive surgery, one would prefer to see the patient on a frequent basis, due to a higher chance at postoperative complications, a more prolonged recovery time and probably a higher need of psychosocial assistence.

The use and duration of follow-up has been questioned over the past few decades[23-27]. Not only in SCC of the OC, but also in other fields of medicine, has it been shown that prescheduled follow-up visits probably do not improve chances at more early detection of recurrent disease. For instance, Ritoe et al.[27] showed that for laryngeal cancer treated primarily by radiotherapy, only 2% of the total number of routine visits revealed subclinical recurrent disease.

Follow-up after curative treatment of oral carcinoma has a number of goals: early identification of recurrent disease or second primary tumors and early curative treatment if possible; psychosocial help, registration of late complications following therapy and evaluation of treatment. The value of follow-up depends largely on certain parameters such as whether a feasible treatment for recurrent disease is available, whether early detection improves patient survival, and whether there is a proper diagnostic test (e.g. good sensitivity/specificity) to rule out recurrent disease.

If we consider these parameters in the context of our study, we have shown that our treatment for recurrent disease only saves 22% of patients with recurrent disease. Our study shows that over half of patients with recurrent disease visit their treating surgeon outside the prescheduled visits. Finally, the diagnostic tests are the same as those used during preoperative staging (inspection, palpation and US [+/- FNAC]) and have the same limitations. Five out of 197 patients benefitted from the detection of their recurrent disease as they survived after salvage treatment. Three of these 5 recurrences were detected at prescheduled follow-up visits, 2 were detected at extra visits on the patients' own request. The necessity and cost-effectiveness of a routine follow-up schedule can thus be questioned as there is a very limited effect on survival. However, from a psychosocial perspective (for instance rehabilitation after extensive surgery) routine follow-up is, of course, valuable, as well as in the evaluation of complications and treatment, especially in patients who underwent extensive reconstructive surgery. Merkx et al.[9] have already called for a reduction in the number of years of follow-up from 10 to 5 years. We would suggest that in curatively treated oral carcinoma, especially in low stage tumors, the number of years of routine follow-up could perhaps be reduced from 5 to 2 years as a next step in limiting prescheduled doctor visits.

Conclusions

Selective neck dissection of level I-III remains a reliable staging procedure in cN0 SCCOC and appears to have therapeutic value as well. There is no indication for a level IV dissection. In case of recurrent disease, survival rates drop dramatically despite treatment. Long-term routine follow-up in case of cN0 oral SCC is of very limited benefit in terms of patient survival and could perhaps be limited to 2 years, leading to more cost-effective postoperative treatment.

Reference List

1. Leemans CR, Tiwari R, Nauta JJ, van dW, I, Snow GB. Regional lymph node involvement and its significance in the development of distant metastases in head and neck carcinoma. *Cancer.* 1993;71:452-456.
2. Leemans CR, Tiwari R, Nauta JJ, van dW, I, Snow GB. Recurrence at the primary site in head and neck cancer and the significance of neck lymph node metastases as a prognostic factor. *Cancer.* 1994;73:187-190.
3. Snow GB, Annyas AA, van Slooten EA, Bartelink H, Hart AA. Prognostic factors of neck node metastasis. *Clin Otolaryngol.* 1982;7:185-192.
4. van den Brekel MW, Castelijns JA, Stel HV et al. Occult metastatic neck disease: detection with US and US-guided fine-needle aspiration cytology. *Radiology.* 1991;180:457-461.
5. van den Brekel MW, Castelijns JA, Reitsma LC, Leemans CR, van dW, I, Snow GB. Outcome of observing the N0 neck using ultrasonographic-guided cytology for follow-up. *Arch Otolaryngol Head Neck Surg.* 1999;125:153-156.
6. Kligerman J, Lima RA, Soares JR et al. Supraomohyoid neck dissection in the treatment of T1/T2 squamous cell carcinoma of oral cavity. *Am J Surg.* 1994;168:391-394.
7. Cunningham MJ, Johnson JT, Myers EN, Schramm VL, Jr., Thearle PB. Cervical lymph node metastasis after local excision of early squamous cell carcinoma of the oral cavity. *Am J Surg.* 1986;152:361-366.
8. Medina JE, Byers RM. Supraomohyoid neck dissection: rationale, indications, and surgical technique. *Head Neck.* 1989;11:111-122.
9. Merkx MA, van Gulick JJ, Marres HA et al. Effectiveness of routine follow-up of patients treated for T1-2N0 oral squamous cell carcinomas of the floor of mouth and tongue. *Head Neck.* 2006;28:1-7.
10. Weiss MH, Harrison LB, Isaacs RS. Use of decision analysis in planning a management strategy for the stage N0 neck. *Arch Otolaryngol Head Neck Surg.* 1994;120:699-702.
11. Manni JJ, van den Hoogen FJ. Supraomohyoid neck dissection with frozen section biopsy as a staging procedure in the clinically node-negative neck in carcinoma of the oral cavity. *Am J Surg.* 1991;162:373-376.
12. van den Hoogen FJ, Manni JJ. Value of the supraomohyoid neck dissection with frozen section analysis as a staging procedure in the clinically negative neck in squamous cell carcinoma of the oral cavity. *Eur Arch Otorhinolaryngol.* 1992;249:144-148.
13. van den Brekel MW. Lymph node metastases: CT and MRI. *Eur J Radiol.* 2000;33:230-238.
14. Stuckensen T, Kovacs AF, Adams S, Baum RP. Staging of the neck in patients with oral cavity squamous cell carcinomas: a prospective comparison of PET, ultrasound, CT and MRI. *J Craniomaxillofac Surg.* 2000;28:319-324.
15. Wensing BM, Vogel WV, Marres HA et al. FDG-PET in the clinically negative neck in oral squamous cell carcinoma. *Laryngoscope.* 2006;116:809-813.
16. Nieuwenhuis EJ, Castelijns JA, Pijpers R et al. Wait-and-see policy for the N0 neck in early-stage oral and oropharyngeal squamous cell carcinoma using ultrasonography-guided cytology: is there a role for identification of the sentinel node? *Head Neck.* 2002;24:282-289.
17. Results of a prospective trial on elective modified radical classical versus supraomohyoid neck dissection in the management of oral squamous carcinoma. Brazilian Head and Neck Cancer Study Group. *Am J Surg.* 1998;176:422-427.

18. Dias FL, Kligerman J, Matos dS et al. Elective neck dissection versus observation in stage I squamous cell carcinomas of the tongue and floor of the mouth. *Otolaryngol Head Neck Surg.* 2001;125:23-29.
19. Keski-Santti H, Atula T, Tornwall J, Koivunen P, Makitie A. Elective neck treatment versus observation in patients with T1/T2 N0 squamous cell carcinoma of oral tongue. *Oral Oncol.* 2006;42:96-101.
20. Kerrebijn JD, Freeman JL, Irish JC et al. Supraomohyoid neck dissection. Is it diagnostic or therapeutic? *Head Neck.* 1999;21:39-42.
21. Byers RM, Weber RS, Andrews T, McGill D, Kare R, Wolf P. Frequency and therapeutic implications of "skip metastases" in the neck from squamous carcinoma of the oral tongue. *Head Neck.* 1997;19:14-19.
22. Shah JP, Candela FC, Poddar AK. The patterns of cervical lymph node metastases from squamous carcinoma of the oral cavity. *Cancer.* 1990;66:109-113.
23. Boysen M, Lovdal O, Tausjo J, Winther F. The value of follow-up in patients treated for squamous cell carcinoma of the head and neck. *Eur J Cancer.* 1992;28:426-430.
24. Cooney TR, Poulsen MG. Is routine follow-up useful after combined-modality therapy for advanced head and neck cancer? *Arch Otolaryngol Head Neck Surg.* 1999;125:379-382.
25. Grau JJ, Cuchi A, Traserra J et al. Follow-up study in head and neck cancer: cure rate according to tumor location and stage. *Oncology.* 1997;54:38-42.
26. de Visscher AV, Manni JJ. Routine long-term follow-up in patients treated with curative intent for squamous cell carcinoma of the larynx, pharynx, and oral cavity. Does it make sense? *Arch Otolaryngol Head Neck Surg.* 1994;120:934-939.
27. Ritoe SC, Krabbe PF, Kaanders JH, van den Hoogen FJ, Verbeek AL, Marres HA. Value of routine follow-up for patients cured of laryngeal carcinoma. *Cancer.* 2004;101:1382-1389.

CHAPTER 6.0

Lymph node density in clinically N0 oral squamous cell carcinoma: does it have predictive value?

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Abstract

Objective

Standard treatment of patients with squamous cell carcinoma of the oral cavity (SCCOC) and a clinically negative (cN0) neck comprises, amongst others, a selective neck dissection. Lymph node density (LND) has recently been shown to be a strong predictor of overall survival and disease-free survival (DFS) in SCCOC. Can LND also predict locoregional control (LRC) and DFS accurately in a cN0 SCCOC cohort?

Methods

In a group of 197 patients with cN0 SCCOC, primary tumor characteristics (location, cT stage, pT stage, perineural growth, angiolymphatic spread, surgical resection margins, degree of differentiation and growing pattern), as well as LND were retrospectively registered. Multivariate analyses were performed to assess the effects of various factors on predicting outcome.

Results

LND had an independent, significant negative influence on LRC ($p<0.001$) and DFS ($p=0.02$) as did diffuse growing pattern and irradical resection borders (LRC, $p=0.099$ and $p<0.001$, respectively; DFS, $p=0.019$ and $p<0.001$, respectively).

Conclusions

LND might be of value in predicting LRC in SCCOC patients with a cN0 neck.

Introduction

Head and neck squamous cell carcinoma is the sixth most commonly occurring type of cancer in the Netherlands. Squamous cell carcinoma of the oral cavity (SCCOC) alone accounts for about 900 new cases a year[1] in the Netherlands and for about 23,000 new cases a year in the United States of America[2]. Treatment of these tumors has gradually changed, over the years, from extensive surgery, including radical neck dissection, to a more selective one. There is growing evidence that in clinically (c) T1N0 tumors, resection of the primary tumor alone, combined with a strict ultrasound-guided fine-needle aspiration cytology (FNAC) follow-up of the neck, has survival rates comparable with patients who had an additional elective neck dissection[3-6]. Treatment in cT2–T4 tumors usually consists of resection of the primary tumor, combined with selective neck dissection (SND) of levels I, II, and III of the ipsilateral neck, even for palpably and radiographically staged negative necks (cN0), as metastatic spread is found in 20–40% of neck dissection specimens[7-10]. A large number of neck dissections are therefore unnecessary. Postoperative radiotherapy can be indicated, based on histopathologic findings.

Nonetheless, in about 20% of patients treated in this fashion, local or regional recurrence occurs during follow-up. A regional recurrence in the selectively dissected neck during follow-up could imply that surgical dissection was not sufficient and that not all the lymphatic tissue was removed; if regional recurrence appears outside the dissected neck, this could imply that the SND should have been more extensive.

Theoretically, one could argue that the more nodes are dissected, the smaller the chance would be that lymphatic tissue can be left behind; in different fields of surgical oncology, it has been shown that more resected nodes resulted in a higher survival rates (both overall survival [OS] and disease-specific survival [DSS])[11-14].

In a small number of studies of SCCOC, the concept of lymph node density (LND) recently has been shown to be a strong predictor of OS and disease-free survival (DFS)[15-17]. LND can be calculated by dividing the number of histopathologically proven metastatic nodes by the total number of lymph nodes found in the resection specimen.

Postoperative treatment and follow-up in SCCOC could perhaps be more specifically adjusted to the individual patient if characteristics such as LND would indicate the patient to be at specific risk of recurrent disease. Postoperative radiotherapy could then, possibly, be more individually applied. Moreover, follow-up visits could be planned more individually, probably leading to a less intensive and less expensive follow-up routine for the majority of patients.

The aim of this study is to evaluate the possible role of histopathologic features with special emphasis on LND in cN0 SCCOC patients with regard to local and regional control (LRC) and DFS.

Patients and methods

The medical records of patients with histopathologically proven SCCOC, who presented at the Radboud University Nijmegen Medical Center between January 1, 1992 and December 1, 2004 were reviewed. All included patients were staged cN0 and were planned for an elective neck dissection of levels I–III (supraomohyoid neck dissection as described by Medina and Byers[18]). All necks were preoperatively examined by means of palpation and ultrasound examination, followed by FNAC on indication (e.g. necrotic core, rounded shape, smallest axial diameter >5 mm). Computed tomography and/or magnetic resonance imaging scans were carried out, depending on indication, to stage the primary tumor. SND was expanded to modified radical neck dissection (MRND) in the case of positive peroperative frozen section sampling (FSS). Patients who had suffered from head and neck squamous cell carcinoma in the 5-year period before treatment were excluded. Follow-up comprised at least 5 years.

Standardized histopathologic examination of the neck dissection specimen consisted of hematoxylin and eosin staining, node count, lymph node slicing (coupes of 4 μm thickness every 2–3 mm) and examination for metastatic disease and extracapsular spread (ECS). Primary tumors were reviewed for pT stage, degree of differentiation, invasion of surgical resection margins (e.g. radically, minimally free, and irradically resected tumors [>5 mm margin, 1–5 mm margin, and irradical respectively]), presence of perineural spread, bone invasion, angio-invasion and/or lymphatic invasion, and presence of diffuse growing patterns. Perineural spread was defined as tumor cells being present in the perineural space or epineurium. Lymphatic and/or vascular invasion was defined as tumor cell invasion of endothelial-lined spaces.

Postoperative radiotherapy was advised in the case of tumor-positive resection margins and/or bone invasion by the tumor and/or 2 or more metastatic lymph nodes and/or the presence of ECS in any node as stated by the Dutch practice guidelines 'Carcinoma of the oral cavity and the oropharynx'[1]. In the presence of 2 or more of the following characteristics, postoperative radiotherapy was indicated as well: 1 metastatic lymph node, close resection margins (<5 mm free of tumor), angio-lymphatic invasion, perineural invasion, and a diffuse growing pattern.

LND was calculated by dividing the number of histopathologically proven metastatic nodes by the total amount of nodes dissected. In the case of bilateral SND I–III, both sides were independently scored. Patients were additionally divided into 3 groups (with an LND <0.06, 0.06–0.13, and >0.13) based on recent studies by Shrime et al.[15] and Gil et al.[16].

Statistical analysis

Histopathologic examination of the neck dissection specimen and follow-up were used as a reference standard. Cox regression was applied to analyze the relationship between

LRC and DFS and potential explanatory variables. The following variables were included in the analysis: surgical resection margins of the primary tumor (radically and marginally free versus irradically resected tumors); presence or absence of perineural spread; angio-invasion and/or lymphatic invasion; a diffuse growing pattern; tumor-positive nodes (found during histopathologic examination of the neck dissection specimen); degree of differentiation; and LND (using 1% LND as unit). To allow comparisons with recent literature, the analyses were repeated with the LND as a variable using the defined categories. Cox regression analysis was applied with backward selection, with a threshold to stay in the model for p-values of 0.10. SPSS 16.0© was used for statistical analysis.

Results

Patient characteristics

A total of 197 patients were included in the study. The majority of tumors (82%) was situated in either the floor of the mouth or the lateral part of the oral tongue and 84% was clinically scored as either T1 or T2. For an overview of patient characteristics, see ***table 1***.

Neck dissections and LND

Twenty-three bilateral neck dissections were performed, of which 21 SNDs of regions I–III (220 necks in total); on 2 occasions, an MRND (due to strong suspicion or proven peroperative metastatic spread by FSS) was combined with an SND I–III of the contralateral neck. In 48 out of 197 cases (49 necks, 24%) metastatic spread was present. One patient had histopathologically proven metastatic spread on both sides of the bilaterally dissected neck.

A total of 3786 nodes were examined: 2072 and 1714 nodes on the right and left side, respectively. The average number of nodes per neck thus was 17, with a range of 4–48 nodes per side of the neck. In 49 pathologically node positive (pN+) necks, the average number of nodes examined was 20 (range 7–48). There were 79 positive nodes in total; on average, 1.6 positive nodes per positive neck. The average LND was 0.10 (10%) in 49 pN+ necks, with a median of 0.06 (6%); ranging from 0.02 to 0.75 (2–75%).

Forty-two of 77 (55%) patients undergoing postoperative radiotherapy had a pN0 neck, so primary tumor characteristics were the main reason for treatment in these cases. In 11 cases, ECS was present (7 times in a pN1 neck, 4 times in a pN2b neck); 6 pN1 necks were irradiated; the other 20 irradiated pN1 necks had no ECS, but characteristics of the primary tumor were the reason for postoperative radiotherapy. Nine patients had N2b necks and were irradiated. Two patients were lost to follow-up because they moved to another area.

Variable	N	%
Gender		
Male	125	63
Female	72	37
cT stage		
T1	64	32
T2	103	52
T3	17	9
T4	13	7
Site		
Lateral tongue	85	43
Floor of mouth	76	39
Retromolar trigone	20	10
Buccal gingiva	5	2
Alveolar process	11	6
Diffuse growing pattern		
Present	66	33.5
Not present	131	66.5
Resection margins		
Radically	100	50.8
Marginally free	67	34.0
Irradical	30	15.2
Grade of differentiation		
Poor	22	11.2
Moderate	148	75.1
Well	27	13.7
Perineural invasion		
Present	56	28.4
Not present	141	71.6
Angio-lymphatic invasion		
Present	29	14.7
Not present	168	85.3
pN Stage and percentage of ECS		
pN0	149	75.6
pN1	33 (7)	16.8 (21.1)
pN2b	14 (4)	7.1 (28.6)
pN2c	1	0.5
LND categories		
0%	149	75.6
<6%	18	9.1
6–13%	22	11.2
>13%	8	4.1

Table 1. Patient characteristics.
cN = clinical N stage; pN = pathological N stage; ECS = extracapsular spread; LND = lymph node density

Locoregional control

Forty patients (20% of patients) had local (n=24), regional (n=14), or distant metastases (n=2). Fourteen of these patients presented with regional recurrence (7% of 197 patients). Of 149 pN0 necks, 9 patients (6%) developed initial regional recurrent disease, while 3 of the 48 patients with pN+ necks (6%) initially presented with regional recurrence. Two more patients presented with regional recurrent disease, but also had a second primary tumor, making the origin of regional disease unclear.

Twenty-four patients initially presented with a local recurrence (12% of 197 patients), while the remaining 2 patients had distant metastatic disease without locoregional disease. Nineteen patients with recurrent disease underwent salvage surgery and 9 of these patients also received additional radiotherapy with curative intent. Six patients received radiotherapy only with curative intent, 1 patient was curatively treated in another hospital and was lost to follow-up. The remaining 14 patients were treated palliatively.

Multivariate Cox regression analysis demonstrated irradical resection borders, a diffuse growing pattern, and LND to be of significant importance concerning the development of recurrent disease (see ***table 2*** and ***figures 1–3*** for details).

	Hazard Ratio	**p-value**	**Lower 95% CI**	**Upper 95% CI**
LND /(%)	1.059	<0.001	1.029	1.090
Irradical resection border	4.15	<0.001	0.124	0.465
Diffuse growing pattern	1.712	0.099	0.904	3.245

Table 2. Resulting end model of Cox regression analysis on LRC

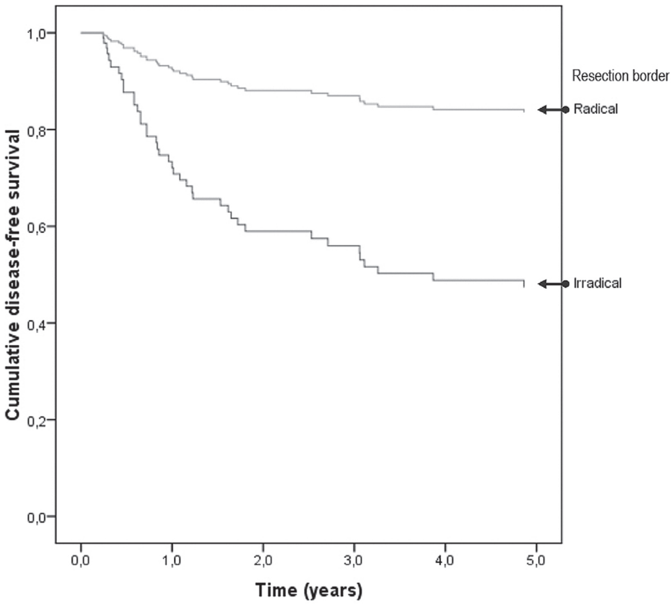

Figure 1. Relation between radicality of the resection border and time to recurrent disease. Curves fitted by Cox regression analysis (p<0.001).

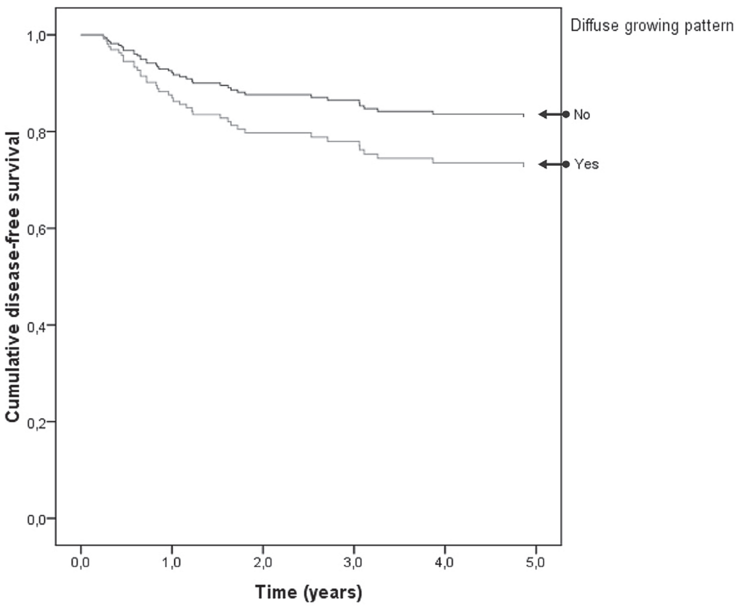

Figure 2. Relationship between the presence of a diffuse growing pattern and time to recurrent disease. Curves fitted by Cox regression analysis (p=0.099).

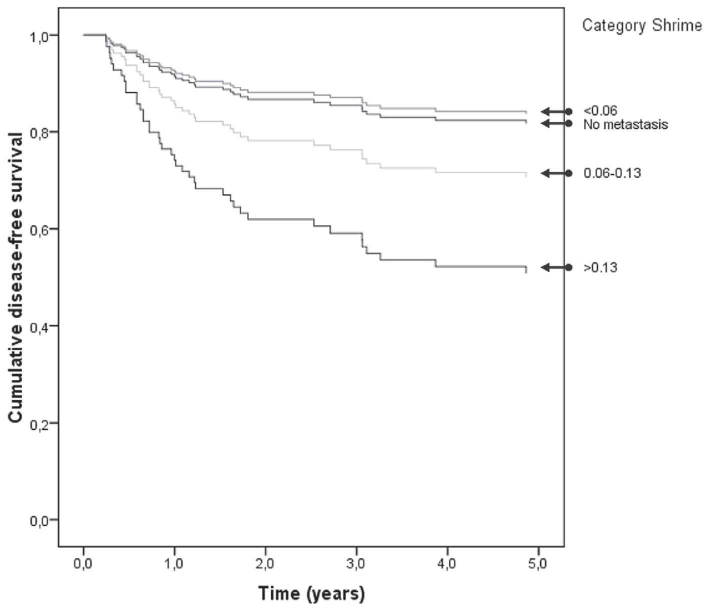

Figure 3. Relationship between categories of LND by Shrime et al.[15] and time to recurrent disease. Curves fitted by Cox regression analysis ($p<0.001$).

Using the cut-off points as propagated by Shrime et al.[15] and Gil et al.[16] regarding LND, one can expect a less successful model, as turning a metric variable into categories reduces the information. This was supported by additional analyses. If the metric variable LND is replaced with the categories as defined by Gil et al.[16], we find a p-value of 0.062 for LND. Using the definition given by Shrime et al.[15], LND would show a p-value of 0.037. In both cases, this is a considerable higher pvalue than that for LND as a metric variable. Note: as the regression model is multiplicative by nature, the effect of a 10% increase in LND, for instance, should be calculated as (hazard ratio [HR] LND)^{10}. So, in this case, one would estimate the chance of a loss of LRC to be increased by a factor of $1.059^{10} = 1.77$ if the LND is 10 percent points higher. The interpretation of the other two variables is simpler. The presence of a diffuse growing pattern is estimated to increase the chance at recurrent disease by a factor 1.712, while an irradical resection increases this chance by a factor of 4.15.

Regarding DFS, multivariate analysis showed LND as a metric variable to lead to a 1.132-fold increased rate (HR) of disease-related death ($p=0.02$). A diffuse growing pattern of the primary tumor showed a 2.453-fold increased rate of a disease-related death ($p=0.019$); irradical resection of the primary tumor showed an increased rate of 6.25 ($p<0.001$) at a disease-related death (see ***table 3*** for the resulting end model of Cox regression analysis).

	Hazard Ratio	p-value	Lower 95% CI	Upper 95% CI
LND /(%)	1.132	0.02	1.047	1.224
Irradical resection border	6.250	<0.001	0.073	0.348
Diffuse growing pattern	2.453	0.019	1.159	5.192
pN+ neck	0.369	0.093	0.115	1.182

Table 3: Resulting end model of Cox regression analysis on DFS

Discussion

In the current study, a group of 197 cN0 patients with SCCOC was retrospectively reviewed to identify the possible predictive value of LND. LND has been shown to be an independent, significant predictive factor for locoregional recurrence and DFS during follow-up with a p-value of <0.001 and 0.02, respectively. The presence of a diffuse growing pattern and irradical resection of the primary tumor were also independent, significant predictive factors regarding LRC and DFS.

The ability to predict tumor behavior in head and neck carcinoma is of great importance, both in pre- and post-treatment decision making. Initial tumor treatment could be more individually adjusted; standardized elective neck dissections in cN0 SCCOC patients could perhaps be abandoned in a number of cases, and postoperative treatment and follow-up could both be individualized.

Our selective group of cN0 SCCOC patients was comparable with other cohorts with regard to male/female ratio, age, distribution of T stage, localization of the tumor, percentage of occult metastatic spread found during histopathologic examination, and development of local and regional recurrent disease[7, 19].

Irradically resected tumors have repeatedly been proven to result in worse local control when compared with radically resected tumors[20, 21] as was marginally free resection of the primary tumor[20] in a smaller number of studies.

Pathologic T stage has, in a number of studies, been shown to be a predictor of recurrent disease and shortened DFS[22, 23], as has the presence of a diffuse growing pattern[24], perineural spread[10, 25, 26], and, sporadically, a poor differentiation of the tumor[27]. In the current study, of these latter factors, only the presence of a diffuse growing pattern could be confirmed as an independent, significant predictor of both LRC and DFS. These findings add to the existing controversy regarding the possible predictive value of primary tumor characteristics.

In different types of cancer, an association between the number of nodes dissected and survival was found[11-14, 28, 29]. The rationale behind the recently mentioned concept of LND is that the more nodes are dissected and histopathologically reviewed, the bigger the chance of finding possible metastatic disease[30] and the higher the prognostic value of the neck dissection would be. Agrama et al.[30] found that the chance of finding metastatic disease in T1/T2 squamous cell carcinoma of the head and neck increased with a higher number of nodes found.

Shrime et al.[15] claimed LND was a 'very important prognostic indicator of survival': as LND increased, survival decreased. They found a strong inverse association of LND with OS. Two cut-off points were found: an LND <6% was associated with the highest OS; patients with an LND of >12.5% had a significantly worse OS. As already mentioned by Shrime et al.[15], there are a number of limitations regarding their recommendations based on the SEER (Surveillance, Epidemiology and End Results) database. First of all, no distinction could be made between different kinds of neck dissection: an SND of levels I–III in a cN0 patient could not be distinguished from a classic radical neck dissection in a patient with preoperative proof of multiple metastases – of course, preoperative estimated survival is already worse for the latter group. Also, the extent of histopathologic review of the neck dissection specimen could not be retrieved: were all nodes sectioned and stained in a standard way? Was immunohistochemistry used in a number of patients? If histopathologic review would be standardized and optimized, perhaps either more nodes would be found and examined (leading to a downgraded LND) or, on the other hand, the same number of nodes would be more thoroughly examined, leading to a higher amount of confirmed metastatic nodes (possibly leading to an upgraded LND). Furthermore, data regarding histopathologic properties of the primary tumor were not available, as was knowledge of recurrence rates and possible postoperative radiotherapy. However, according to the authors, due to the large number and large heterogeneity of the included patients, the 'generalizability' of their conclusions would be possible.

A recent study by Gil et al.[16] included 386 patients treated for SCCOC (of which 219 were scored pN0), who all had a standardized MRND of levels I–IV or I–V. In the pN+ cohort, LND was found to be significantly associated with OS and DSS: LND ≤6% 5-year OS rate was 58% versus 28% for patients with LND >6% ($p<0.01$). DSS was 65% versus 34% in these respective groups. Multivariate analysis confirmed that LND was the single most influential factor on DSS. Regarding our current study, the finding that in Gil et al.'s[16] subgroup of patients who had an SND (cN0), LND also was the most significant predictor of outcome ($p<0.04$) is of importance. Moreover, there was no change in LND when therapeutic neck dissection was compared with SND. The authors rightly emphasize that in case of more selective standard neck dissections in cN0 patients, it might be estimated that LND will be even higher.

Our cohort consisted of cN0 patients who underwent SNDs of levels I–III in the vast majority, with a nodal yield of 17 that was well below the average yield (35) in the cohort of Gil et al.[16], who performed MRND. Shrime et al.[15] assumed that the concept of LND might be subject to debate in cN0. However, our statistical analysis did point out a highly significant predictive value of LND in the cN0 SCCOC patient regarding LRC and DFS. The concept of LND might be a welcome additional prognosticator in the field of head and neck squamous cell carcinoma. Of course, one could argue that LND is a modification of already known and used prognostic factors, such as the pN stage. In the Dutch practice guidelines 'Carcinoma of the oral cavity and oropharynx',[1] the decision to treat a dissected neck postoperatively is based, for instance, on the number of metastatic nodes found: a neck containing 1 metastatic node without ECS basically does not have to be treated, while a neck containing 2 or more tumor-positive nodes will have to be treated (by radiotherapy). When the concept of LND is applied, this would lead to the following thoughts: if an SND I–III would yield, on average, 20 nodes and a MRND would yield 35 nodes, one could estimate that in the case of 1 tumor-positive node (without ECS) LND would be 5% and 3%, respectively. However, if another node would be tumor-positive, LND would rise to 10% and 6%, respectively, and chance at LRC would drop significantly. Using the pN stage, postoperative radiotherapy would, in either case, be advised. However, in the case of smaller numbers of nodes dissected, one would more readily advise postoperative treatment when compared with pN staging (for instance when 1 metastatic node is found in 10–15 dissected nodes [LND 10–7%]; according to the guidelines no additional treatment would be necessary, but based on LND, treatment should be given).

A number of limitations from this study should be addressed. Unfortunately, the number of patients in whom the tumor depth was registered was too small to include this as a variable in our analysis, although a number of studies stress the importance of this factor regarding LRC and/or survival (both overall and disease-free)[31-33]. Another renowned predictor of LRC and DFS, the presence of ECS in lymph node metastasis[23, 24], also was not included in our analysis because the number of cases was too small. This latter factor is most likely due to our cohort being cN0. Also, a clear distinction between the effect of either local or regional recurrences could not be made, due to the small number of patients remaining in each group weakening the statistical value.

Given the thoughts above, we believe that the concept of LND might be promising, also in cN0 cohorts, albeit mainly in patients with only 1 metastatic lymph node and a small number of dissected nodes, because postoperative radiotherapy is already advised (according to the guidelines) for 2 or more metastatic lymph nodes. We believe more research is needed: more homogeneous patient populations should be investigated, histopathologic research techniques should be mentioned as should any postoperative treatment. In time, LND could be a useful additional factor in determining possible postoperative treatment and follow-up routine in SCCOC.

Conclusions

The predictability of LRC in cN0 SCCOC remains a difficult issue: if tumor behavior could be estimated, treatment and follow-up could be better adjusted to individual patients. Positive resection margins and a diffuse growing pattern in our cohort significantly influenced LRC and DFS negatively, as did LND. The concept of LND might be promising in predicting LRC and DFS in patients suffering from cN0 SCCOC and could, in time, be a useful additional factor in determining a patient's postoperative treatment and follow-up routine.

Reference List

1. Knegt PP, Keus RB, Roodenburg JL. [The practice guideline 'Carcinoma of the oral cavity and oropharynx']. Ned Tijdschr Geneeskd 2006 Jan 14;150(2):83-8.
2. American Cancer Society. Cancer Facts and Figures 2008.
3. Wensing BM, Merkx MA, de Wilde PC, et al. Assessment of preoperative ultrasonography of the neck and elective neck dissection in patients with oral squamous cell carcinoma. Oral Oncol 2010 Feb;46(2):87-91.
4. van den Brekel MW, Castelijns JA, Reitsma LC, et al. Outcome of observing the N0 neck using ultrasonographic-guided cytology for follow-up. Arch Otolaryngol Head Neck Surg 1999 Feb;125(2):1536.
5. van den Brekel MW, Reitsma LC, Quak JJ, et al. Sonographically guided aspiration cytology of neck nodes for selection of treatment and follow-up in patients with N0 head and neck cancer. AJNR Am J Neuroradiol 1999 Oct;20(9):1727-31.
6. Nieuwenhuis EJ, Castelijns JA, Pijpers R, et al. Wait-and-see policy for the N0 neck in early-stage oral and oropharyngeal squamous cell carcinoma using ultrasonography-guided cytology: is there a role for identification of the sentinel node? Head Neck 2002 Mar;24(3):282-9.
7. Results of a prospective trial on elective modified radical classical versus supraomohyoid neck dissection in the management of oral squamous carcinoma. Brazilian Head and Neck Cancer Study Group. Am J Surg 1998 Nov;176(5):422-7.
8. van den Hoogen FJ, Manni JJ. Value of the supraomohyoid neck dissection with frozen section analysis as a staging procedure in the clinically negative neck in squamous cell carcinoma of the oral cavity. Eur Arch Otorhinolaryngol 1992;249(3):144-8.
9. Stuckensen T, Kovacs AF, Adams S, et al. Staging of the neck in patients with oral cavity squamous cell carcinomas: a prospective comparison of PET, ultrasound, CT and MRI. J Craniomaxillofac Surg 2000 Dec;28(6):319-24.
10. Clark JR, Naranjo N, Franklin JH, et al. Established prognostic variables in N0 oral carcinoma. Otolaryngol Head Neck Surg 2006 Nov;135(5):748-53.
11. Bando E, Yonemura Y, Taniguchi K, et al. Outcome of ratio of lymph node metastasis in gastric carcinoma. Ann Surg Oncol 2002 Oct;9(8):775-84.
12. Berger AC, Sigurdson ER, LeVoyer T, et al. Colon cancer survival is associated with decreasing ratio of metastatic to examined lymph nodes. J Clin Oncol 2005 Dec 1;23(34):8706-12.
13. Chan JK, Kapp DS, Cheung MK, et al. The impact of the absolute number and ratio of positive lymph nodes on survival of endometrioid uterine cancer patients. Br J Cancer 2007 Sep 3;97(5):605-11.
14. Sierzega M, Popiela T, Kulig J, et al. The ratio of metastatic/resected lymph nodes is an independent prognostic factor in patients with node-positive pancreatic head cancer. Pancreas 2006 Oct;33(3):240-5.
15. Shrime MG, Ma C, Gullane PJ, et al. Impact of nodal ratio on survival in squamous cell carcinoma of the oral cavity. Head Neck 2009 Sep;31(9):1129-36.
16. Gil Z, Carlson DL, Boyle JO, et al. Lymph node density is a significant predictor of outcome in patients with oral cancer. Cancer 2009 Dec 15;115(24):5700-10.
17. Ebrahimi A, Clark JR, Zhang WJ, et al. Lymph node ratio as an independent prognostic factor in oral squamous cell carcinoma. Head Neck 2010 Oct 21.

18. Medina JE, Byers RM. Supraomohyoid neck dissection: rationale, indications, and surgical technique. Head Neck 1989 Mar;11(2):111-22.
19. Zbaren P, Nuyens M, Caversaccio M, et al. Elective neck dissection for carcinomas of the oral cavity: occult metastases, neck recurrences, and adjuvant treatment of pathologically positive necks. Am J Surg 2006 Jun;191(6):756-60.
20. Chen TY, Emrich LJ, Driscoll DL. The clinical significance of pathological findings in surgically resected margins of the primary tumor in head and neck carcinoma. Int J Radiat Oncol Biol Phys 1987 Jun;13(6):833-7.
21. Parsons JT, Mendenhall WM, Stringer SP, et al. An analysis of factors influencing the outcome of postoperative irradiation for squamous cell carcinoma of the oral cavity. Int J Radiat Oncol Biol Phys 1997 Aug 1;39(1):137-48.
22. Patel RS, Clark JR, Dirven R, et al. Prognostic factors in the surgical treatment of patients with oral carcinoma. ANZ J Surg 2009 Jan;79(1-2):19-22.
23. Leemans CR, Tiwari R, Nauta JJ, et al. Recurrence at the primary site in head and neck cancer and the significance of neck lymph node metastases as a prognostic factor. Cancer 1994 Jan 1;73(1):187-90.
24. Ravasz LA, Slootweg PJ, Hordijk GJ, et al. The status of the resection margin as a prognostic factor in the treatment of head and neck carcinoma. J Craniomaxillofac Surg 1991 Oct;19(7):314-8.
25. Fagan JJ, Collins B, Barnes L, et al. Perineural invasion in squamous cell carcinoma of the head and neck. Arch Otolaryngol Head Neck Surg 1998 Jun;124(6):637-40.
26. Rahima B, Shingaki S, Nagata M, et al. Prognostic significance of perineural invasion in oral and oropharyngeal carcinoma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2004 Apr;97(4):423-31.
27. Liao CT, Lin CY, Fan KH, et al. Identification of a High-Risk Group Among Patients With Oral Cavity Squamous Cell Carcinoma and pT1-2N0 Disease. Int J Radiat Oncol Biol Phys 2010 Nov 13.
28. Weir L, Speers C, D'yachkova Y, et al. Prognostic significance of the number of axillary lymph nodes removed in patients with node-negative breast cancer. J Clin Oncol 2002 Apr 1;20(7):1793-9.
29. Tepper JE, O'Connell MJ, Niedzwiecki D, et al. Impact of number of nodes retrieved on outcome in patients with rectal cancer. J Clin Oncol 2001 Jan 1;19(1):157-63.
30. Agrama MT, Reiter D, Cunnane MF, et al. Nodal yield in neck dissection and the likelihood of metastases. Otolaryngol Head Neck Surg 2003 Feb;128(2):185-90.
31. O'Brien CJ, Lauer CS, Fredricks S, et al. Tumor thickness influences prognosis of T1 and T2 oral cavity cancer--but what thickness? Head Neck 2003 Nov;25(11):937-45.
32. Spiro RH, Huvos AG, Wong GY, et al. Predictive value of tumor thickness in squamous carcinoma confined to the tongue and floor of the mouth. Am J Surg 1986 Oct;152(4):345-50.
33. Sparano A, Weinstein G, Chalian A, et al. Multivariate predictors of occult neck metastasis in early oral tongue cancer. Otolaryngol Head Neck Surg 2004 Oct;131(4):472-6.

CHAPTER 7.0

Summary, Conclusions and future perspectives

Treatment of the neck in squamous cell carcinoma of the oral cavity (SCCOC) has changed over the past decades. However, controversy still exists regarding the treatment of the clinically negative neck (cN0 neck). The choice between (s)elective neck dissection (SND) and watchful waiting (accompanied by for instance the use of ultrasound (US +/- fine needle aspiration cytology [FNAC]) during follow-up nowadays still is a difficult one, mainly due to the low sensitivities of preoperative staging techniques. If a technique can repeatedly and in different institutions lower the amount of false-negative neck stagings to 20% or less (confirmed by postoperative histopathological examination), elective neck dissections in case of cN0 SCCOC could be abandoned[1].

The aim of this thesis was firstly to retrospectively analyze the results of our own routine preoperative staging by US (+/- FNAC) of the cN0 neck in SCCOC (**Chapter 2**). In the search for more accurate preoperative staging techniques in **Chapters 3 and 4** we prospectively evaluated the use of fluoro deoxy glucose-positron emission tomography (FDG-PET) and a new magnetic resonance imaging (MRI) contrast agent (ultra small particles of iron oxide [USPIO]) in cN0 SCCOC respectively.

In **Chapter 5** our standard follow-up routine in cN0 SCCOC is analyzed. **Chapter 6** handles possible prognosticators found by histopathological examination that could be able to influence management of the N0 neck in SCCOC.

Summary of results

Chapter 2

In our retrospective chart analysis of 224 patients suffering from cN0 SCCOC we found a false-negative rate of 22% for US (+/- FNAC). This finding indicates that in our center the use of US (+/- FNAC) approaches the proposed 20% false-negative rate by Weiss et al.[1] Our percentage compares favorably with a number of studies promoting the preoperative use of CT and/or MRI in neck staging and are in line with a recent meta-analysis by de Bondt et al.[2] The Dutch National Guideline for oral and oropharyngeal SCC advocates the use of US (+/- FNAC) to stage the neck[3]. In European studies it has repeatedly been shown that US (+/- FNAC) in cN0 SCC shows an at least comparable percentage of false-negative findings when compared to CT and MRI-scanning[2, 4-6]. We strongly advocate the use of US (+/- FNAC) in preoperative staging of the cN0 neck in SCCOC. In our series the metastatic part in occult metastatic nodes was very small: over 80% had a smallest diameter between 0 and 5 mm. This small size explains why the nodes containing them will be difficult to find by any kind of preoperative imaging evaluation. Of course, standard histopathological techniques can be upgraded (for instance by routinely performing multislice sectioning and immunohistochemistry) which would perhaps lead to the discovery of more metastases[7].

Clinically T1N0M0 SCCOC showed significantly less occult metastatic spread than cT2N0M0 SCCOC (10 versus 29%). Based on the criteria of Weiss et al.[1], elective neck dissection could be abandoned in cT1N0M0 SCCOC.

Chapter 3

Prospective analysis of FDG-PET scanning in cN0 SCCOC showed a disappointingly low sensitivity, specificity and accuracy in 28 consecutive patients (33, 76 and 63% respectively). Main explanation is probably the small size of metastatic parts in occult nodes (average diameter of 4.3mm), which also causes difficulties while using the 'standard' preoperative imaging techniques such as US (+/- FNAC), CT and/or MRI. In **Chapter 2** we already mentioned that in a larger group of patients also the smallest diameter of metastatic parts in tumor-involved lymph nodes was between 0 and 5 mm in more than 80% of cases. We conclude that FDG-PET, mainly due to presence of micrometastatic spread, probably is not suitable as a substitution for any known preoperative imaging technique in staging the palpably negative neck in SCCOC. This finding recently was confirmed in a meta-analysis by Kyzas et al.[8] evaluating 32 studies with cN0/cN+ HNSCC patients: it was estimated that overall sensitivity was 79% and specificity was 86%. However, in cN0 necks sensitivity only reached 50% (specificity was 87%).

Chapter 4

Our prospective pilot-analysis of USPIO-enhanced MRI in 11 cN0 SCCOC patients showed a large amount of false-positive results. Only one lymph node was true-positive: however, this node was missed by US (+/- FNAC), PET-CT and MRI. Although in cancer of the prostate for instance it has proven (by this technique) to be possible to identify tumor-positive lymph nodes with a minimal diameter of 2 to 3 millimeters[9, 10], in the cN0 neck this technique seems less favourable. However, by performing a node-to-node analysis we estimated a very high negative predictive value (NPV) and sensitivity for USPIO MRI (100% for both). When combined with US (+/- FNAC) with a reknown high specificity in our center, it would seem possible to refrain from neck dissection in a number of patients. More research regarding this optional combination is mandatory as is examination of possible explanations for the high amount of false-positive results. In its current form, USPIO-enhanced MRI is unsuitable as a single preoperative staging technique in patients suffering from cN0 SCCOC.

Chapter 5

One-hundred-and-ninety-seven patients suffering from cN0 SCCOC were analyzed after 5 years of follow-up. Five-year disease-free survival was 67% and comparable to percentages mentioned by other authors. Eighty-three percent of recurrent disease was diagnosed within 2 years; 53% of patients suffering from recurrent disease visited their physician outside the routine follow-up schedule with complaints leading to the finding of recurrent disease. This is in line with findings in different kinds of cancers but has not yet been mentioned in SCCOC and leads to questions regarding the length and intensity of prescheduled follow-up. As mentioned by many other authors, there are only few survivors after recurrent disease (in our study 78% of patients with recurrence die due to their recurrence). Only 3 patients (of 5 in total who could be salvaged and survived) presented during prescheduled follow-up visits. We concluded that standard follow-up in (cN0) SCCOC in a tertiary referral center could perhaps be limited from 5 to 2 years with regards to the finding of recurrent disease. Of course other aspects of follow-up (other than the finding of recurrent disease) like psychological support and guidance for the patient will have to be weighed in individual patients before advising to limit routine visits.

Chapter 6

We retrospectively reviewed the predictive capacities of histopathological parameters in 197 patients with special emphasis on the concept of lymph node density (LND). LND can be calculated by dividing the number of histopathologically proven metastatic nodes by the total number of lymph nodes found in the resection specimen and has in a small number of studies shown to significantly influence overall and disease-free survival[11, 12].

Multivariate analysis showed irradical resection borders, a diffuse growing pattern of the tumor and LND to have significant negative influence on locoregional control (LRC) and disease-free survival (DFS). These factors have been mentioned by different authors, as well as for instance angiolymphatic invasion, perineural growth, extracapsular spread, stage of the primary tumor, occult metastatic spread, grade of tumor differentiation and tumor depth[11-24].

Intensity of postoperative treatment (e.g. radiotherapeutic treatment) is currently adjusted based on histopathological findings. When reviewing the literature considering prognostic or predictive value of histopathological characteristics there is no consensus on a number of these characteristics, despite many retrospective analyses that have been performed. Ideally, a diagnostic technique being able to predict (future) tumor behaviour would be used before operating on the patient: extent of tumoral resection and type of neck dissection (if necessary) and possibly follow-up routine could be adjusted individually. Regarding primary tumor characteristics we believe that the use of biomarkers in predicting tumoral behaviour seems more promising due to the greater representativety and reproducability. However, development of a universally applicable tumor gene expression set will take some time; in the mean time the concept of LND could be a useful additional factor in adjusting postoperative treatment and follow-up routine in a select group of patients.

Conclusions and future perspectives

Ultrasound (+/- FNAC) in our institution repeatedly has proven to be a reliable preoperative staging technique in cN0 SCCOC[4, 25]. While searching for a preoperative imaging technique being able to outperform US (+/- FNAC), FDG-PET and USPIO-enhanced MRI in its current form show no improvement in staging the cN0 neck in SCCOC. The (ultra-) small size of metastatic deposits explains these findings regarding FDG-PET. In case of USPIO-enhanced MRI more research is needed to identify reasons as to why this technique in the cN0 neck reveals a large amount of false positive findings, in contrast to findings in for instance prostate carcinoma[9].

When applying the criteria as posed by Weiss et al.[1], the 'golden standard' in staging the neck in T2-T4N0M0 SCCOC currently remains the selective neck dissection of levels I-III (former supraomohyoid neck dissection) in our institution. Clinically T1N0M0 SCCOC can be treated by excision of the primary tumor alone; if done so, the neck should be carefully followed in time (with the use of US [+/- FNAC]). Future application of the concept of sentinel lymph node biopsy (SLNB) in small (T1/T2N0) tumors of the oral cavity in our institution is currently being considered. This concept in a multi-center study showed a sensitivity of 93% in 134 T1/T2N0 SCCOC and oropharyngeal cancer patients[26]. Paleri et al. in their meta-analyis confirmed a sensitivity of 94%[27]. In a recent review by Stoeckli et al.[28] it was stated that 'either SLNB or SLNB assisted SND has the potential to become a new standard of care for staging and treatment of cN0 neck in patients with early SCCOC.'

The possibility to predict tumoral behaviour by means of analyzing characteristics of the primary tumor would probably lead to more individually adjusted treatment of the (cN0) neck. However, too much controversy in recent literature exists regarding the use of histopathological parameters in choosing between watchful waiting and treatment of the cN0 neck in SCCOC. Our study added to that controversy. We believe that the development of a genetic profile of SCCOC will be more easily applicable and reproducable and that future research regarding prediction of tumor behaviour should focus on this specific area. Currently a multicenter application of the genetic profile as reported by Roepman et al.[29] is being analyzed. The concept of LND might in the meantime be a useful additional factor in determining postoperative treatment in a small group of cN0 SCCOC patients.

Five year disease-specific survival in cN0 SCCOC reaches 67%. Routine follow-up visits can be limited to 2 years after treatment of cN0 SCCOC instead of the currently used 5 years, based amongst others on the fact that the majority of recurrent disease presents within 2 years from treatment and salvage treatment of recurring disease is difficult. With a more reliable staging technique and a subsequently more individually adjusted treatment we believe that disease specific survival can be raised.

Upcoming staging techniques like the use of for instance SLNB will probably cause a further decline in the use of SND, as will the growing knowledge of DNA-profiles of SCCOC.

Reference List

1. Weiss MH, Harrison LB, Isaacs RS. Use of decision analysis in planning a management strategy for the stage N0 neck. Arch Otolaryngol Head Neck Surg 1994 Jul;120(7):699-702.
2. de Bondt RB, Nelemans PJ, Hofman PA, et al. Detection of lymph node metastases in head and neck cancer: a meta-analysis comparing US, USgFNAC, CT and MR imaging. Eur J Radiol 2007 Nov;64(2):266-72.
3. Knegt PP, Keus RB, Roodenburg JL. [The practice guideline 'Carcinoma of the oral cavity and oropharynx']. Ned Tijdschr Geneeskd 2006 Jan 14;150(2):83-8.
4. van den Hoogen FJ, Manni JJ. Value of the supraomohyoid neck dissection with frozen section analysis as a staging procedure in the clinically negative neck in squamous cell carcinoma of the oral cavity. Eur Arch Otorhinolaryngol 1992;249(3):144-8.
5. van den Brekel MW, Castelijns JA, Stel HV, et al. Modern imaging techniques and ultrasound-guided aspiration cytology for the assessment of neck node metastases: a prospective comparative study. Eur Arch Otorhinolaryngol 1993;250(1):11-7.
6. van den Brekel MW, Reitsma LC, Quak JJ, et al. Sonographically guided aspiration cytology of neck nodes for selection of treatment and follow-up in patients with N0 head and neck cancer. AJNR Am J Neuroradiol 1999 Oct;20(9):1727-31.
7. Brouwer J, de Bree R, Comans EF, et al. Positron emission tomography using [18F]fluorodeoxyglucose (FDG-PET) in the clinically negative neck: is it likely to be superior? Eur Arch Otorhinolaryngol 2004 Oct;261(9):479-83.
8. Kyzas PA, Evangelou E, axa-Kyza D, et al. 18F-fluorodeoxyglucose positron emission tomography to evaluate cervical node metastases in patients with head and neck squamous cell carcinoma: a meta-analysis. J Natl Cancer Inst 2008 May 21;100(10):712-20.
9. Heesakkers RA, Hovels AM, Jager GJ, et al. MRI with a lymph-node-specific contrast agent as an alternative to CT scan and lymph-node dissection in patients with prostate cancer: a prospective multicohort study. Lancet Oncol 2008 Sep;9(9):850-6.
10. Barentsz JO, Futterer JJ, Takahashi S. Use of ultrasmall superparamagnetic iron oxide in lymph node MR imaging in prostate cancer patients. Eur J Radiol 2007 Sep;63(3):369-72.
11. Gil Z, Carlson DL, Boyle JO, et al. Lymph node density is a significant predictor of outcome in patients with oral cancer. Cancer 2009 Dec 15;115(24):5700-10.
12. Shrime MG, Ma C, Gullane PJ, et al. Impact of nodal ratio on survival in squamous cell carcinoma of the oral cavity. Head Neck 2009 Sep;31(9):1129-36.
13. Spiro RH, Huvos AG, Wong GY, et al. Predictive value of tumor thickness in squamous carcinoma confined to the tongue and floor of the mouth. Am J Surg 1986 Oct;152(4):345-50.
14. Pentenero M, Gandolfo S, Carrozzo M. Importance of tumor thickness and depth of invasion in nodal involvement and prognosis of oral squamous cell carcinoma: a review of the literature. Head Neck 2005 Dec;27(12):1080-91.
15. Leemans CR, Tiwari R, Nauta JJ, et al. Recurrence at the primary site in head and neck cancer and the significance of neck lymph node metastases as a prognostic factor. Cancer 1994 Jan 1;73(1):187-90.

16. Chen TY, Emrich LJ, Driscoll DL. The clinical significance of pathological findings in surgically resected margins of the primary tumor in head and neck carcinoma. Int J Radiat Oncol Biol Phys 1987 Jun;13(6):833-7.
17. Parsons JT, Mendenhall WM, Stringer SP, et al. An analysis of factors influencing the outcome of postoperative irradiation for squamous cell carcinoma of the oral cavity. Int J Radiat Oncol Biol Phys 1997 Aug 1;39(1):137-48.
18. Patel RS, Clark JR, Dirven R, et al. Prognostic factors in the surgical treatment of patients with oral carcinoma. ANZ J Surg 2009 Jan;79(1-2):19-22.
19. Ravasz LA, Slootweg PJ, Hordijk GJ, et al. The status of the resection margin as a prognostic factor in the treatment of head and neck carcinoma. J Craniomaxillofac Surg 1991 Oct;19(7):314-8.
20. Fagan JJ, Collins B, Barnes L, et al. Perineural invasion in squamous cell carcinoma of the head and neck. Arch Otolaryngol Head Neck Surg 1998 Jun;124(6):637-40.
21. Rahima B, Shingaki S, Nagata M, et al. Prognostic significance of perineural invasion in oral and oropharyngeal carcinoma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2004 Apr;97(4):423-31.
22. Liao CT, Lin CY, Fan KH, et al. Identification of a High-Risk Group Among Patients With Oral Cavity Squamous Cell Carcinoma and pT1-2N0 Disease. Int J Radiat Oncol Biol Phys 2010 Nov 13.
23. Sparano A, Weinstein G, Chalian A, et al. Multivariate predictors of occult neck metastasis in early oral tongue cancer. Otolaryngol Head Neck Surg 2004 Oct;131(4):472-6.
24. O'Brien CJ, Lauer CS, Fredricks S, et al. Tumor thickness influences prognosis of T1 and T2 oral cavity cancer--but what thickness? Head Neck 2003 Nov;25(11):937-45.
25. Wensing BM, Merkx MA, de Wilde PC, et al. Assessment of preoperative ultrasonography of the neck and elective neck dissection in patients with oral squamous cell carcinoma. Oral Oncol 2010 Feb;46(2):87-91.
26. Ross GL, Soutar DS, Gordon MD, et al. Sentinel node biopsy in head and neck cancer: preliminary results of a multicenter trial. Ann Surg Oncol 2004 Jul;11(7):690-6.
27. Paleri V, Rees G, Arullendran P, et al. Sentinel node biopsy in squamous cell cancer of the oral cavity and oral pharynx: a diagnostic meta-analysis. Head Neck 2005 Sep;27(9):739-47.
28. Stoeckli SJ, Alkureishi LW, Ross GL. Sentinel node biopsy for early oral and oropharyngeal squamous cell carcinoma. Eur Arch Otorhinolaryngol 2009 Jun;266(6):787-93.
29. Roepman P, Wessels LF, Kettelarij N, et al. An expression profile for diagnosis of lymph node metastases from primary head and neck squamous cell carcinomas. Nat Genet 2005 Feb;37(2):182-6.

CHAPTER 8.0

Samenvatting

Het plaveiselcelcarcinoom van de mondholte van het squameuze type ('squamous cell carcinoma of the oral cavity [SCCOC]') komt voor bij ongeveer 500 nieuwe patiënten per jaar in Nederland[1] (0,9% van alle soorten kanker in Nederland). Roken en het gebruik van alcohol zijn predisponerende factoren voor het ontwikkelen van dit type kanker[2-4]. De behandeling van deze tumor is in principe chirurgisch. Het SCCOC metastaseert als eerste naar de nabije lymfeklieren in de hals aan de kant van het lichaam waar ook de primaire tumor zit. Het hebben van lymfekliermetastasen is de belangrijkste voorspeller voor de overleving[5, 6]. Hierom is het vroegtijdig opsporen en adequaat behandelen van halskliermetastasen van groot belang.
De meest interessante groep patiënten met een vastgesteld SCCOC betreft de patiënten die met gebruikmaking van de momenteel gangbare stadiëringstechnieken geen aantoonbare metastasen in de hals hebben ('cN0 hals'); uit literatuur blijkt dat in deze groep patiënten bij ongeveer 25-30% toch sprake blijkt van metastasen[7-9], die met behulp van een operatie, waarbij een aantal lymfeklieren uit de hals verwijderd en daaropvolgend histopathologisch onderzocht wordt, wel aangetoond kunnen worden. Er bestaat een internationale consensus gebaseerd op een beslissingsanalyse[10], waarin beschreven staat dat wanneer het percentage preoperatief niet detecteerbare ('klinisch occulte') metastasen onder de 20% gebracht kan worden, er afgezien kan worden van een nu standaard uitgevoerde stadiërende beperkte (selectieve) halsklierdissectie van halsregio's I t/m III (selectieve halsklierdissectie [SHKD] I-III).
Deze groep van patiënten met een cN0 SCCOC, is het onderwerp van deze dissertatie. De onderzoeken beschreven in dit proefschrift proberen een antwoord te krijgen op een aantal vragen, waarbij de zoektocht naar een goed toe te passen preoperatieve stadiëringstechniek die het aantal occulte metastasen onder de 20% brengt, centraal staat.

Na een korte bespreking van de epidemiologie, etiologie en anatomie wordt in de **Inleiding (Hoofdstuk 1)** besproken welke technieken er voorhanden zijn om metastasen in de hals aan te tonen danwel uit te sluiten. De geschiedenis van de halsklierdissectie wordt besproken aangezien een SHKD met daarop volgend histopathologisch onderzoek op dit moment nog steeds de 'gouden standaard' is voor het opsporen van eventueel occult aanwezige halskliermetastasen bij patiënten met een cN0 SCCOC. Vervolgens worden de meest gangbare preoperatieve technieken besproken. De niet-invasieve technieken palpatie, echografisch onderzoek (ultrasound [US]), de computed tomography (CT) en magnetic resonance imaging (MRI) scan en de fluoro deoxy glucose positron emission tomography (FDG-PET) scan worden besproken. Tevens worden twee (minimaal) invasieve technieken besproken: US aangevuld met dunne naald aspiratie cytologie (fine needle aspiration cytology [FNAC]) en de sentinel lymph node biopsy (SLNB). Tot slot wordt kort ingegaan op de voorspellende waarde van histopathologische kenmerken van het SCCOC en de mogelijke (toekomstige) rol van een genetisch profiel, welke voorspellend zouden kunnen zijn voor het gedrag van dit soort tumoren.

In **Hoofdstuk 2** beschrijven we een retrospectieve analyse van 224 patiënten die behandeld zijn in het UMC St Radboud voor een cN0 SCCOC met palpatie en US (+/- FNAC) voorafgaand aan de SHKD I-III. We vonden in 22% van de gevallen metastasen bij het postoperatieve histopathologische onderzoek: het eerder genoemde streefgetal van 20% wordt met behulp van palpatie en US (+/- FNAC) dus benaderd binnen onze kliniek. De gevonden metastasen bleken in 80% van de gevallen kleiner te zijn dan 5 mm in doorsnede; dit verklaart onzes inziens waarom eigenlijk alle huidige beeldvormende modaliteiten grote moeite hebben met het aantonen van niet palpabele metastasen. Voorts vonden we voor kleine tumoren (T1, ongeacht locatie) een beduidend lager percentage aan occulte metastasen dan voor T2 tumoren (10 versus 29% respectievelijk). Het lijkt er dus zeer sterk op dat in geval van een cT1N0M0 SCCOC er afgezien kan worden van de standaard stadiërende selectieve halsklierdissectie.

In **Hoofdstuk 3** voerden we een prospectieve analyse uit van de preoperatieve stadiëring met behulp van de FDG-PET scan bij 28 patiënten met een cN0 SCCOC, welke vervolgens op de gebruikelijke wijze (palpatie en US [+/- FNAC], gevolgd door SHKD I-III) gestadiëerd en behandeld werden. Wederom bleek de gemiddelde minimale diameter van de gevonden metastasen met 4.3 mm erg beperkt en dit gegeven droegen wij aan als voornaamste reden om de matige sensitiviteit, specificiteit en accuracy (33, 76 en 63% respectievelijk) te verklaren. Wij concludeerden dan ook dat, voornamelijk gezien de te verwachten zeer kleine metastasen in deze selectieve patiëntengroep, de FDG-PET scan niet geschikt is voor het verfijnen van de stadiëring van de cN0 hals.

Hoofdstuk 4 behandelt een prospectieve pilot study naar een nieuw contrastmiddel gebruikt bij MRI scans: ultra small particles of iron oxide (USPIO). Toepassing hiervan binnen het UMC St Radboud heeft bij het prostaatcarcinoom geleid tot een daling van het aantal occulte metastasen en daarmee het afschaffen van de electieve klierdissectie in het kleine bekken[11, 12]. Bij 11 patiënten met een cN0 SCCOC werd slechts 1 klier als terecht positief gescoord; een veelvoud daarvan was vals positief. Een 'node-by-node' analyse toonde een zeer hoge negatief voorspellende waarde (NVW) en sensitiviteit aan van 100%. Een mogelijke combinatie met US (+/- FNAC), waarbij juist een hoge specificiteit gehaald kan worden, zou in de toekomst mogelijk kunnen leiden tot het afzien van de standaard SHKD bij patiënten waarbij zowel USPIO-MRI als US (+/- FNAC) geen aanwijzingen voor metastasen laat zien. Als enige preoperatieve stadiëringsmethode lijkt USPIO-MRI bij cN0 SCCOC ongeschikt.

In **Hoofdstuk 5** wordt de 5-jaars-follow-up van een groep van 197 patiënten met een cN0 SCCOC onder de loep genomen. Ziektevrije 5-jaars-overleving was 67% voor deze groep patiënten. Drieëntachtig procent van alle recidieven (lokaal danwel regionaal) blijkt zich binnen 2 jaar te openbaren. Van de mensen met een lokaal danwel regionaal recidief blijkt 53% zich op eigen gelegenheid, dus buiten de reguliere controleafspraken om, te melden met klachten die leiden tot de ontdekking van het recidief. Dit is voor deze groep patiënten nog niet eerder beschreven en leidt tot vragen aangaande de reguliere follow-up-visites: moeten deze patiënten met deze frequentie komen? Moeten we ze wel 5 jaar controleren? Hierbij blijkt tevens dat 78% van alle patiënten met een lokaal, danwel regionaal recidief uiteindelijk, onafhankelijk van het type behandeling voor hun recidief, overlijdt. Hieruit concluderen wij dat het standaard follow-up schema binnen een tertiair oncologisch centrum mogelijk aangepast kan worden: van 5 naar 2 jaar van reguliere controles lijkt vanuit het oogpunt van overleving een reële optie. Uiteraard zullen andere belangrijke zaken als psychosociale aspecten eveneens meegenomen moeten worden bij toekomstige afwegingen.

In **Hoofdstuk 6** beschrijven we in retrospect de voorspellende waarde van histopathologische kenmerken bij 197 patiënten met een cN0 SCCOC, met speciale aandacht voor het concept van de 'lymfeklier dichtheid' (lymph node density, [LND]). De LND kan berekend worden door het aantal bewezen (met behulp van histopathologisch onderzoek) metastatische lymfeklieren te delen door het totaal aantal gevonden lymfeklieren in een geopereerde hals. Deze LND heeft in een aantal studies bewezen een significante invloed te hebben op de overleving (zowel overall als ziektespecifiek) van patiënten met (onder anderen) een mondholtetumor[13,14]. Een multivariate analyse bij onze groep patienten toont aan dat een irradicale resectie van de tumor, een sprieterig groeipatroon van de tumor en de LND allen een verhoogde kans op een recidief en tevens een verlaging van de ziektevrije overleving geven. Deze factoren zijn allen door andere auteurs genoemd, evenals een aantal andere histologische kenmerken van de primaire tumor en de geopereerde hals, welke in onze analyse niet van significante waarde waren of niet bekeken konden worden: bloed- of lymfevatinvasie, stadium van de primaire tumor, tumordifferentiatie, perineurale groei van de tumor, tumordiepte, de aanwezigheid van metastasen in de hals en extracapsulaire verspreiding van tumor buiten een metastase[6, 13-24].
Het ondergaan van en de intensiteit van een post-operatieve behandeling (radiotherapie) is momenteel gebaseerd op aanwezigheid van (een aantal van) deze eerder genoemde kenmerken. Over de waarde van een aantal van deze genoemde kenmerken van de primaire tumor echter bestaat in de literatuur geen consensus ondanks een grote hoeveelheid aan uitgevoerde (met name) retrospectieve studies. Idealiter zou in de diagnostische fase een test bestaan, waarmee het gedrag van een tumor beter ingeschat kan worden; hiermee zou een behandelplan gemaakt kunnen worden dat specifiek op die ene patiënt is gericht. 'Maatwerk' zou hiermee mogelijk zijn en mogelijk kunnen leiden tot een flinke afname van het aantal verrichte electieve halsklierdissecties en mogelijk ook tot een aangepast follow-up schema. Wij geloven dat 'maatwerk' mogelijk op termijn mogelijk zal zijn; hoogstwaarschijnlijk zal het gebruik van zogenaamde 'biomarkers' (een genetisch profiel van een tumor) hierin

een (veel) grotere rol spelen dan de hierboven omschreven histologische kenmerken van de primaire tumor. Voordat er een panklaar en universeel toepasbaar genprofiel beschikbaar zal zijn, zal er nog wel wat tijd verstrijken: in die tussenliggende periode zou het concept van de LND mogelijk een bruikbare additionele factor zijn in het postoperatieve behandel- en follow-upschema bij chirurgisch behandelde patiënten met een cN0 mondholtecarcinoom.

Conclusies

Het gebruik van US (+/- FNAC) heeft binnen onze kliniek bewezen nog steeds tot één van de meest betrouwbare preoperatieve stadiëringsmethoden bij cN0 SCCOC te behoren[8, 25]. Op zoek naar een techniek die ertoe zou kunnen leiden af te zien van de standaard uitgevoerde stadiërende halsklierdissectie, lijken FDG-PET en USPIO MRI niet in staat om deze te vervangen en het percentage patiënten met occulte metastasen in deze groep categorisch onder de 20 procent te brengen. In het geval van FDG-PET lijkt de verklaring voor het matige presteren te liggen in het beperkte volume van de gemiste metastasen. Wat betreft de USPIO MRI hebben we geen duidelijke verklaring kunnen vinden voor het grote aantal vals-positieve bevindingen in cN0 SCCOC. Meer onderzoek zal hiernaar nodig zijn, evenals een studie naar een combinatie met US (+/- FNAC) als preoperatieve stadiëringscombinatie; dit in verband met de zeer hoge NVW en sensitiviteit van USPIO MRI en juist de hoge specificiteit van US (+/- FNAC). Gezien de kleine (10%) kans op occulte metastasen, ongeacht de locatie van de tumor en het afwezig blijven van significant meer recidieven in deze groep, kan afgezien worden van een standaard SHKD I-III bij cT1N0 SCCOC. In T2-T4 tumoren blijft een SHKD I-III behoren tot de standaard behandeling. De mogelijkheid van het toepassen van het concept van SLNB in het geval van T1-T2 tumoren wordt momenteel overwogen binnen onze kliniek.

Wat betreft de follow-up van deze groep cN0 SCCOC patiënten is gebleken dat, gericht op survival, de standaard follow-up van 5 jaar met routine controles teruggebracht zou kunnen worden naar 2 jaar, aangezien verreweg de meeste recidieven binnen 2 jaar optreden en patiënten in meer dan de helft van de gevallen zelf aan de bel trekken met klachten leidend tot de ontdekking van een recidief.

Onze studie identificeerde een 3-tal kenmerken van primaire tumoren (en de geopereerde hals) die leidden tot een significant hogere kans op ontwikkeling van een recidief en verlaging van de ziektespecifieke overleving (irradicale resectie van de tumor, een sprieterige groeiwijze van de tumor en LND); het concept van de LND zou mogelijk voor een kleine groep patiënten kunnen leiden tot een meer 'op maat gemaakte' postoperatieve behandeling.

Wij achten de kans op het succesvol ontwikkelen van een genetisch profiel (een aantal

DNA-kenmerken van tumorcellen wat voorspelt hoe een bepaalde tumor zich zal gedragen) van tumoren groot en denken dat toekomstige inspanningen bij het zoeken naar een bepaalde 'voorspelbaarheid' en daarmee meer individuele behandeling van patiënten met bijvoorbeeld SCCOC, in deze richting zou moeten zijn.

Reference List

1. Knegt PP, Keus RB, Roodenburg JL. [The practice guideline 'Carcinoma of the oral cavity and oropharynx']. Ned Tijdschr Geneeskd 2006 Jan 14;150(2):83-8.
2. Schildt EB, Eriksson M, Hardell L, et al. Oral snuff, smoking habits and alcohol consumption in relation to oral cancer in a Swedish case-control study. Int J Cancer 1998 Jul 29;77(3):341-6.
3. Blot WJ, McLaughlin JK, Winn DM, et al. Smoking and drinking in relation to oral and pharyngeal cancer. Cancer Res 1988 Jun 1;48(11):3282-7.
4. de SE, Boffetta P, Oreggia F, et al. Smoking patterns and cancer of the oral cavity and pharynx: a case-control study in Uruguay. Oral Oncol 1998 Sep;34(5):340-6.
5. Snow GB, Annyas AA, van Slooten EA, et al. Prognostic factors of neck node metastasis. Clin Otolaryngol 1982 Jun;7(3):185-92.
6. Leemans CR, Tiwari R, Nauta JJ, et al. Recurrence at the primary site in head and neck cancer and the significance of neck lymph node metastases as a prognostic factor. Cancer 1994 Jan 1;73(1):187-90.
7. Pitman KT, Johnson JT, Myers EN. Effectiveness of selective neck dissection for management of the clinically negative neck. Arch Otolaryngol Head Neck Surg 1997 Sep;123(9):917-22.
8. van den Hoogen FJ, Manni JJ. Value of the supraomohyoid neck dissection with frozen section analysis as a staging procedure in the clinically negative neck in squamous cell carcinoma of the oral cavity. Eur Arch Otorhinolaryngol 1992;249(3):144-8.
9. Myers LL, Wax MK, Nabi H, et al. Positron emission tomography in the evaluation of the N0 neck. Laryngoscope 1998 Feb;108(2):232-6.
10. Weiss MH, Harrison LB, Isaacs RS. Use of decision analysis in planning a management strategy for the stage N0 neck. Arch Otolaryngol Head Neck Surg 1994 Jul;120(7):699-702.
11. Heesakkers RA, Hovels AM, Jager GJ, et al. MRI with a lymph-node-specific contrast agent as an alternative to CT scan and lymph-node dissection in patients with prostate cancer: a prospective multicohort study. Lancet Oncol 2008 Sep;9(9):850-6.
12. Barentsz JO, Futterer JJ, Takahashi S. Use of ultrasmall superparamagnetic iron oxide in lymph node MR imaging in prostate cancer patients. Eur J Radiol 2007 Sep;63(3):369-72.
13. Shrime MG, Ma C, Gullane PJ, et al. Impact of nodal ratio on survival in squamous cell carcinoma of the oral cavity. Head Neck 2009 Sep;31(9):1129-36.
14. Gil Z, Carlson DL, Boyle JO, et al. Lymph node density is a significant predictor of outcome in patients with oral cancer. Cancer 2009 Dec 15;115(24):5700-10.
15. Spiro RH, Huvos AG, Wong GY, et al. Predictive value of tumor thickness in squamous carcinoma confined to the tongue and floor of the mouth. Am J Surg 1986 Oct;152(4):345-50.
16. Pentenero M, Gandolfo S, Carrozzo M. Importance of tumor thickness and depth of invasion in nodal involvement and prognosis of oral squamous cell carcinoma: a review of the literature. Head Neck 2005 Dec;27(12):1080-91.
17. Chen TY, Emrich LJ, Driscoll DL. The clinical significance of pathological findings in surgically resected margins of the primary tumor in head and neck carcinoma. Int J Radiat Oncol Biol Phys 1987 Jun;13(6):833-7.

18. Parsons JT, Mendenhall WM, Stringer SP, et al. An analysis of factors influencing the outcome of postoperative irradiation for squamous cell carcinoma of the oral cavity. Int J Radiat Oncol Biol Phys 1997 Aug 1;39(1):137-48.
19. Patel RS, Clark JR, Dirven R, et al. Prognostic factors in the surgical treatment of patients with oral carcinoma. ANZ J Surg 2009 Jan;79(1-2):19-22.
20. Ravasz LA, Slootweg PJ, Hordijk GJ, et al. The status of the resection margin as a prognostic factor in the treatment of head and neck carcinoma. J Craniomaxillofac Surg 1991 Oct;19(7):314-8.
21. Fagan JJ, Collins B, Barnes L, et al. Perineural invasion in squamous cell carcinoma of the head and neck. Arch Otolaryngol Head Neck Surg 1998 Jun;124(6):637-40.
22. Rahima B, Shingaki S, Nagata M, et al. Prognostic significance of perineural invasion in oral and oropharyngeal carcinoma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2004 Apr;97(4):423-31.
23. Liao CT, Lin CY, Fan KH, et al. Identification of a High-Risk Group Among Patients With Oral Cavity Squamous Cell Carcinoma and pT1-2N0 Disease. Int J Radiat Oncol Biol Phys 2010 Nov 13.
24. O'Brien CJ, Lauer CS, Fredricks S, et al. Tumor thickness influences prognosis of T1 and T2 oral cavity cancer--but what thickness? Head Neck 2003 Nov;25(11):937-45.
25. Wensing BM, Merkx MA, de Wilde PC, et al. Assessment of preoperative ultrasonography of the neck and elective neck dissection in patients with oral squamous cell carcinoma. Oral Oncol 2010 Feb;46(2):87-91.

Dankwoord

Curriculum Vitae

Dankwoord

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Ik hou van je.

Curriculum Vitae

Bart Matthijs Wensing werd op 11 april 1979 geboren te Arnhem. In 1997 slaagde hij voor het eindexamen Gymnasium op het Stedelijk Gymnasium Arnhem. Hierna kon hij meteen beginnen aan de studie Geneeskunde te Nijmegen, waar hij in november 2003 zijn artsenbul uitgereikt kreeg. Naar aanleiding van een keuze-coschap KNO-heelkunde in het Rijnstate ziekenhuis Arnhem en een wetenschappelijke stage in het UMC St Radboud Nijmegen op het gebied van de KNO-heelkunde was de interesse voor 'de KNO' geboren. Begin 2004 werd hij aangenomen (per maart 2004) als arts-onderzoeker met uitzicht op een opleidingsplaats KNO aan het UMC St Radboud Nijmegen. Na een jaar onderzoek, wat uiteindelijk geleid heeft tot dit proefschrift, werd op 14 maart 2005 aangevangen met de opleiding tot KNO-arts, welke op 14 maart 2010 afgerond werd.
Na een reis door Zuid-Amerika volgend op de afronding van zijn opleiding is hij per 1 juli 2010 begonnen met een fellowship hoofd/hals oncologie aan het UMC St Radboud Nijmegen. De verwachting is dat hij dit fellowship op 1 juli 2012 zal afronden en toe zal treden tot de maatschap Keel-, Neus- en Oorheelkunde en Heelkunde van het Hoofd-/ Halsgebied van het Rijnstate ziekenhuis te Arnhem.
Bart heeft een relatie met Linda Driesse, die op het moment van schrijven van dit curriculum vitae zwanger is van hun eerste kindje.

Stellingen behorende bij het proefschrift 'The clinically negative neck in oral squamous cell carcinoma An update on preoperative imaging and follow-up'

1. Het echografisch onderzoek van de hals, al dan niet aangevuld met een cytologische punctie, heeft over de jaren heen bewezen de meest betrouwbare preoperatieve beeldvormende techniek te zijn in geval van een palpatoir negatieve hals bij patiënten met een mondholtecarcinoom. *(Dit proefschrift)*

2. Het uitvoeren van een electieve halsklierdissectie zou in het geval van een klinische T1N0 mondholtetumor achterwege gelaten kunnen worden. *(Dit proefschrift)*

3. Het regelmatig missen van klinisch occulte metastasen bij mondholtetumoren bij gebruik van gangbare radiologische entiteiten is voor een groot deel te verklaren door de zeer beperkte afmetingen van het metastatische deel in de lymfeklier. *(Dit proefschrift)*

4. Moderne beeldvormingstechnieken zoals FDG-PET scanning en toevoegen van USPIO bij MRI scanning zorgen preoperatief niet voor een betere detectie van occulte metastasen bij mondholtetumoren. *(Dit proefschrift)*

5. De standaard followup bij patiënten met een mondholtetumor zou mogelijk verder ingekort kunnen worden van 5 naar 2 of 3 jaar. *(Dit proefschrift)*

6. In afwachting van routinematig te gebruiken tumormarkers is de Lymph Node Density mogelijk een nieuwe additionele waarde die gebruikt kan worden voor het voorspellen van locoregionale controle en ziektespecifieke overleving bij chirurgisch behandelde mondholtetumoren. *(Dit proefschrift)*

7. Een wetenschapper is een bijzondere vogel: eerst broedt hij en vervolgens legt hij een ei. *(Ferwerda)*

8. De meeste ziekten gaan vanzelf over, als je er maar niet op tijd bij bent. *(Nederlandse dokterswijsheid)*

9. Rookworst zonder R is ook worst. *(Biek Peters)*

10. Oogletsels bij squash kunnen worden voorkomen door de bal voortdurend in het oog te houden.

11. Na het spel gaan de koning en de pion in hetzelfde doosje. *(Italiaans spreekwoord)*

12. Als tijd geld is, hoe arm ben je dan als je géén tijd hebt.